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Fig 1

A

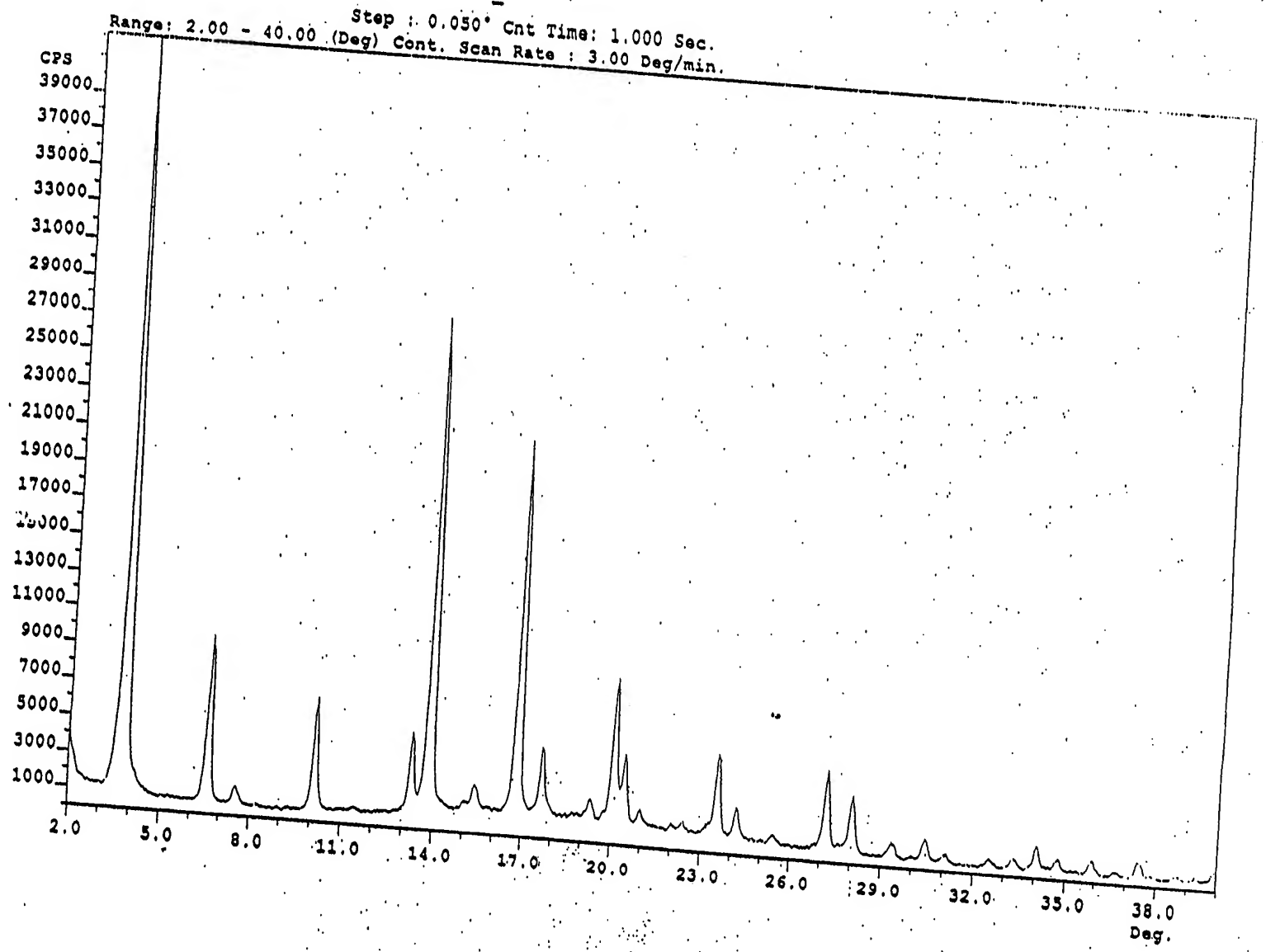

Range: 2.00 - 40.00 (Deg)
Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
39000
37000
35000
33000
31000
29000
27000
25000
23000
21000
19000
17000
13000
11000
9000
7000
5000
3000
1000
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

FIG. 2 C

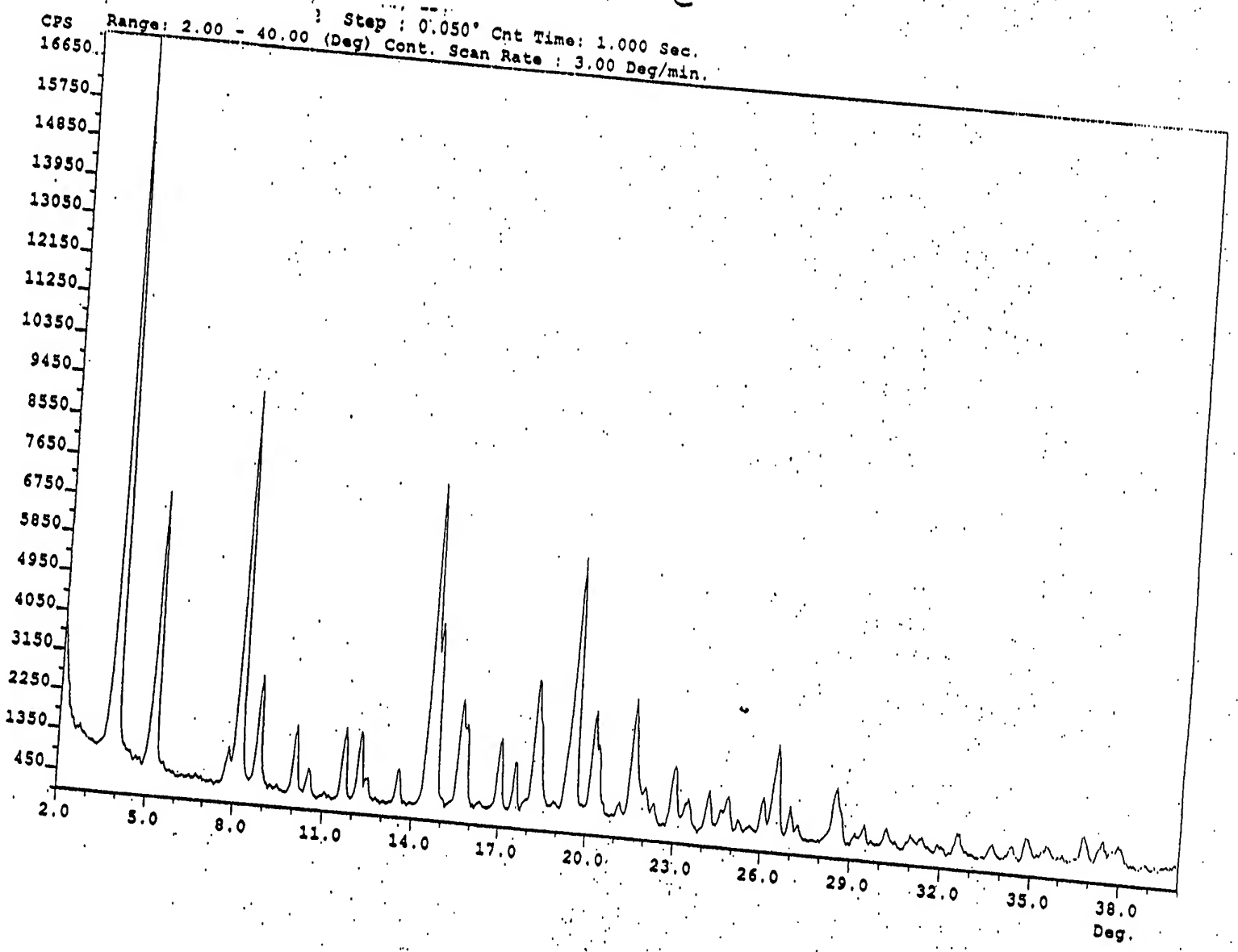

CPS
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
Step : 0.050° Cnt Time: 1.000 Sec.
16650
15750
14850
13950
13050
12150
11250
10350
9450
8550
7650
6750
5850
4950
4050
3150
2250
1350
450
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig 3 D

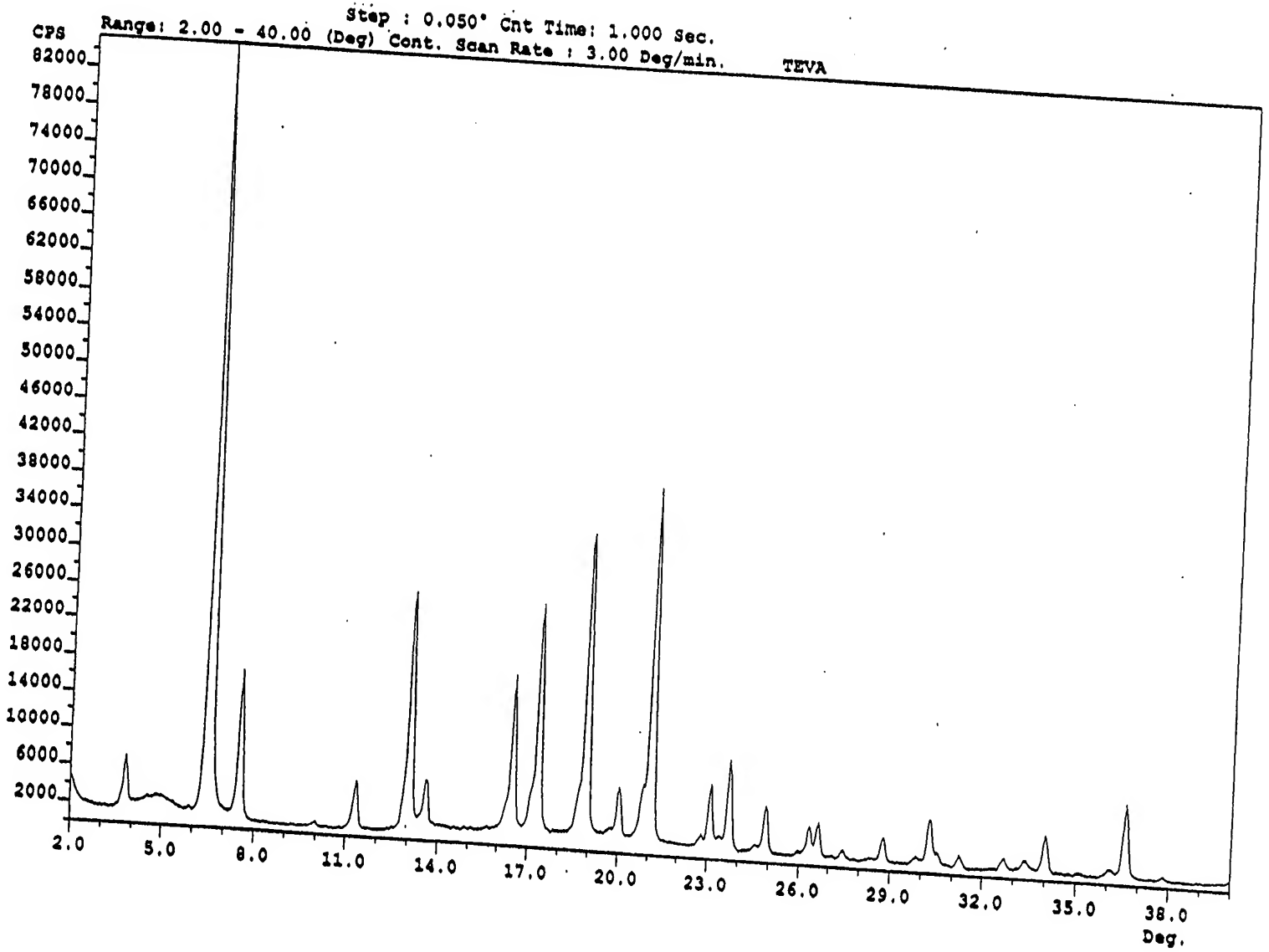

Step : 0.050° Cnt Time: 1.000 Sec.
CPS
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
82000
78000
74000
70000
66000
62000
58000
54000
50000
46000
42000
38000
34000
30000
26000
22000
18000
14000
10000
6000
2000
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

fig 4 .E

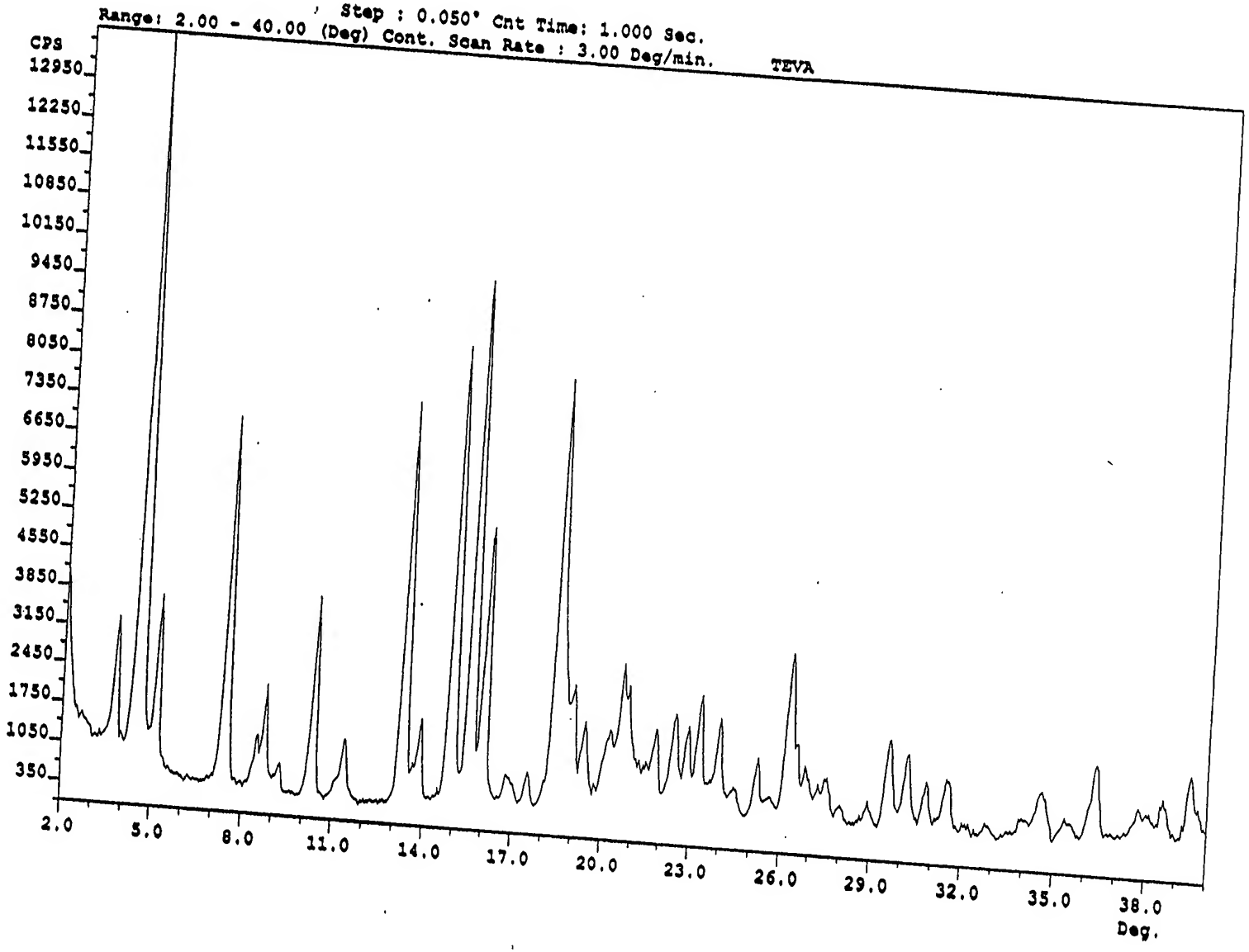

Range: 2.00 - 40.00 (Deg)
Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
12950
12250
11550
10850
10150
9450
8750
8050
7350
6650
5950
5250
4550
3850
3150
2450
1750
1050
350
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 5

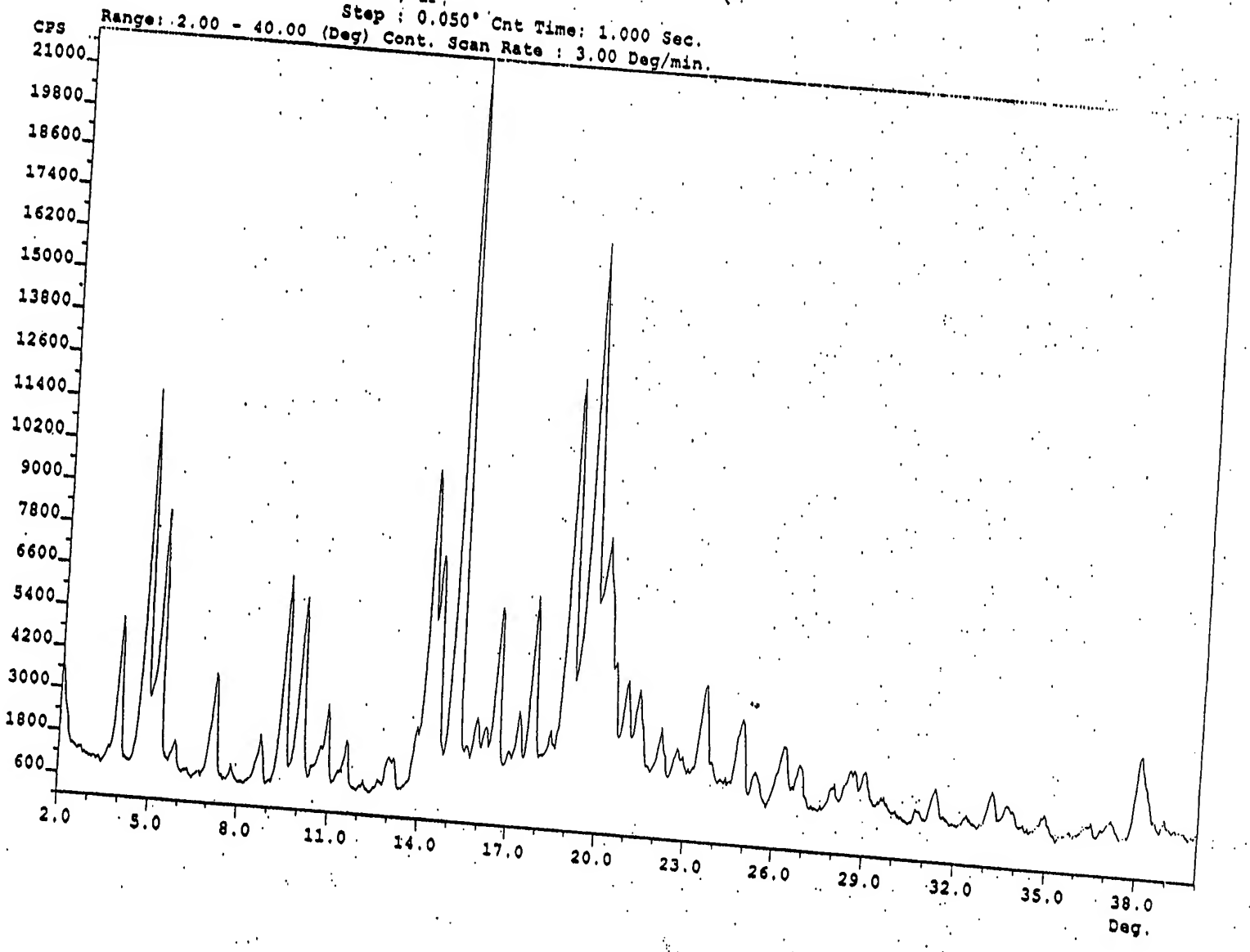

Range: 2.00 - 40.00 (Deg)
Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
21000
19800
18600
17400
16200
15000
13800
12600
11400
10200
9000
7800
6600
5400
4200
3000
1800
600
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 6

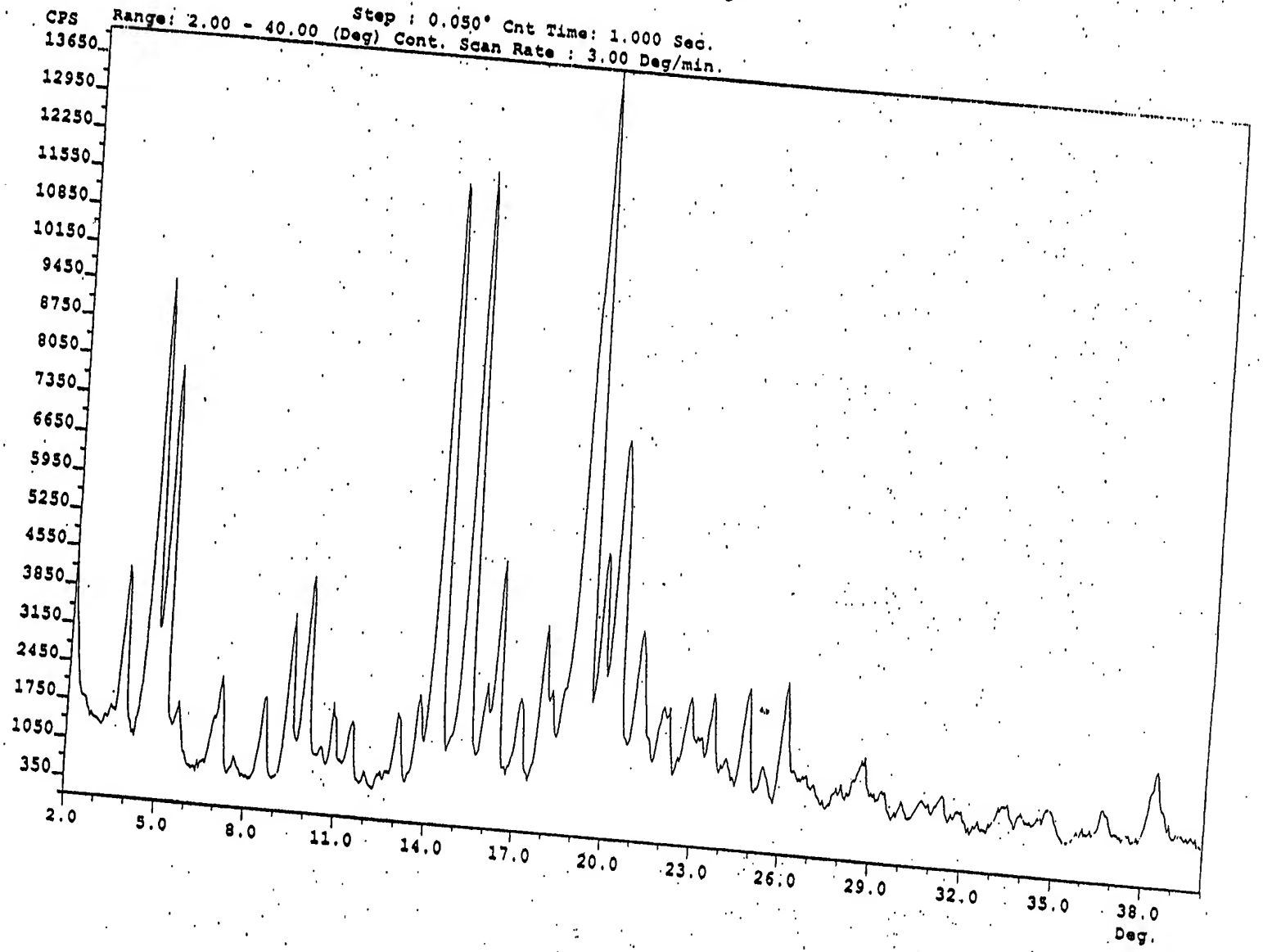

CPS
Range: 2.00 - 40.00 (Deg)
Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
13650
12950
12250
11550
10850
10150
9450
8750
8050
7350
6650
5950
5250
4550
3850
3150
2450
1750
1050
350
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig 7

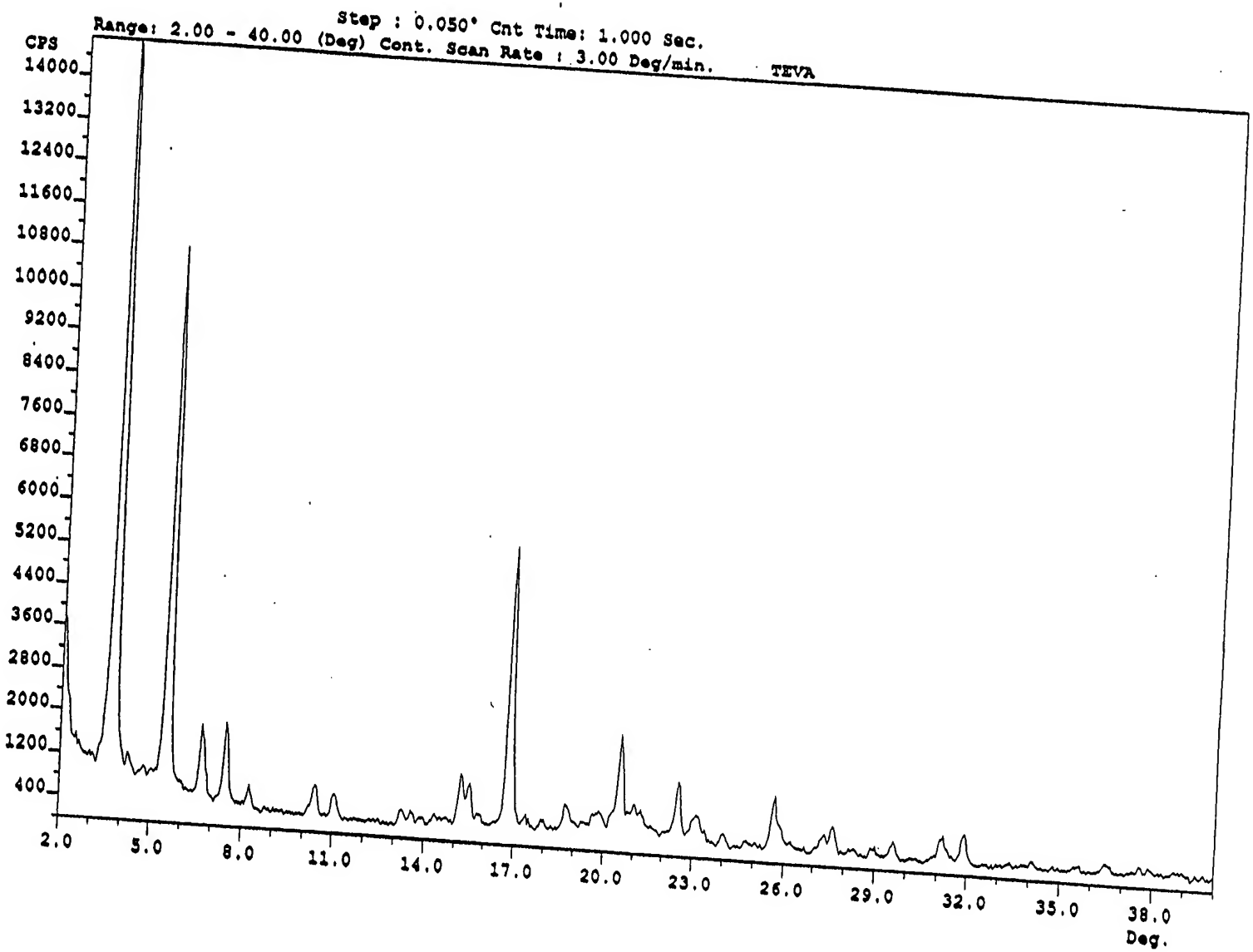

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
14000
13200
12400
11600
10800
10000
9200
8400
7600
6800
6000
5200
4400
3600
2800
2000
1200
400
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 8

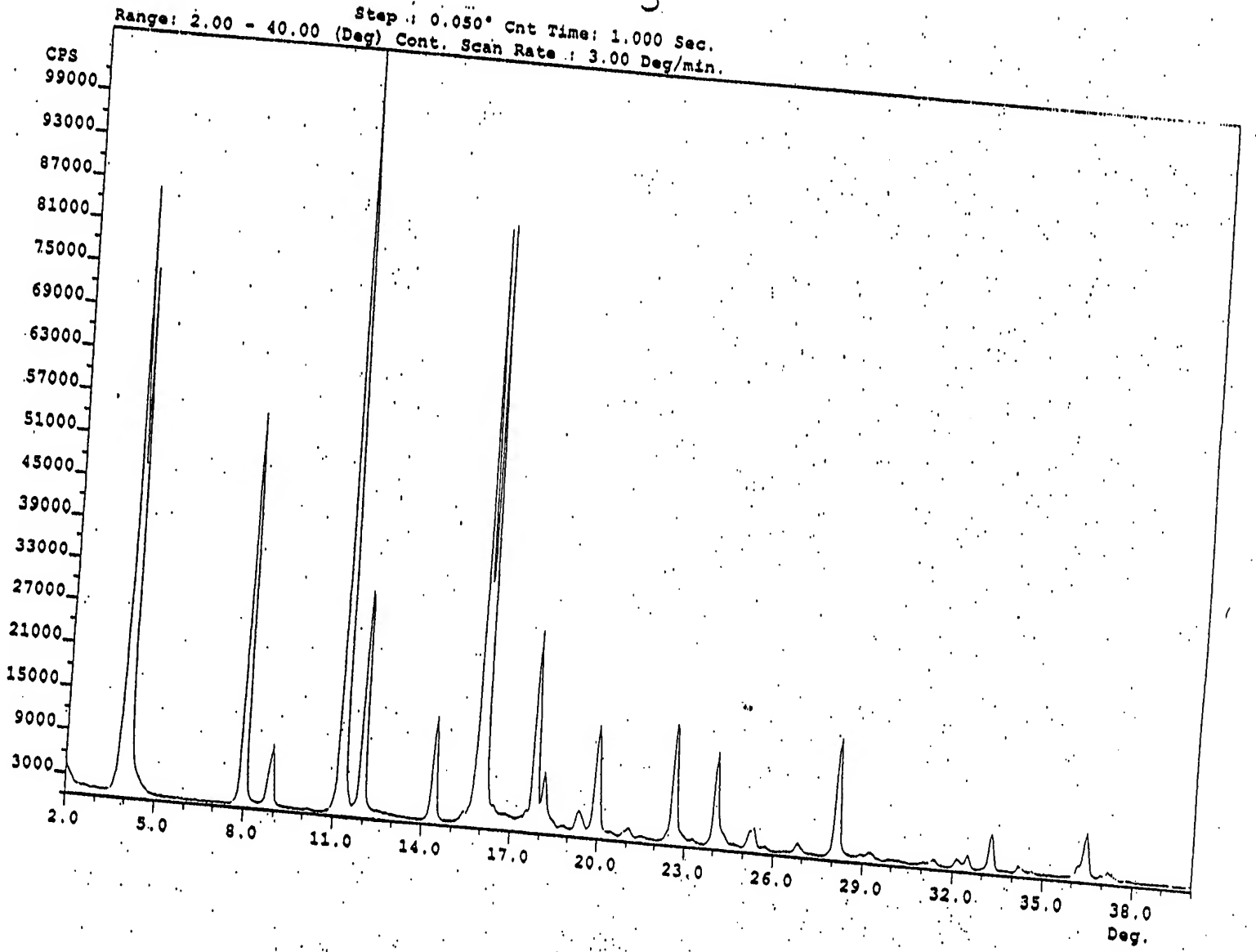

Range: 2.00 - 40.00 (Deg) Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
99000
93000
87000
81000
75000
69000
63000
57000
51000
45000
39000
33000
27000
21000
15000
9000
3000
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 9

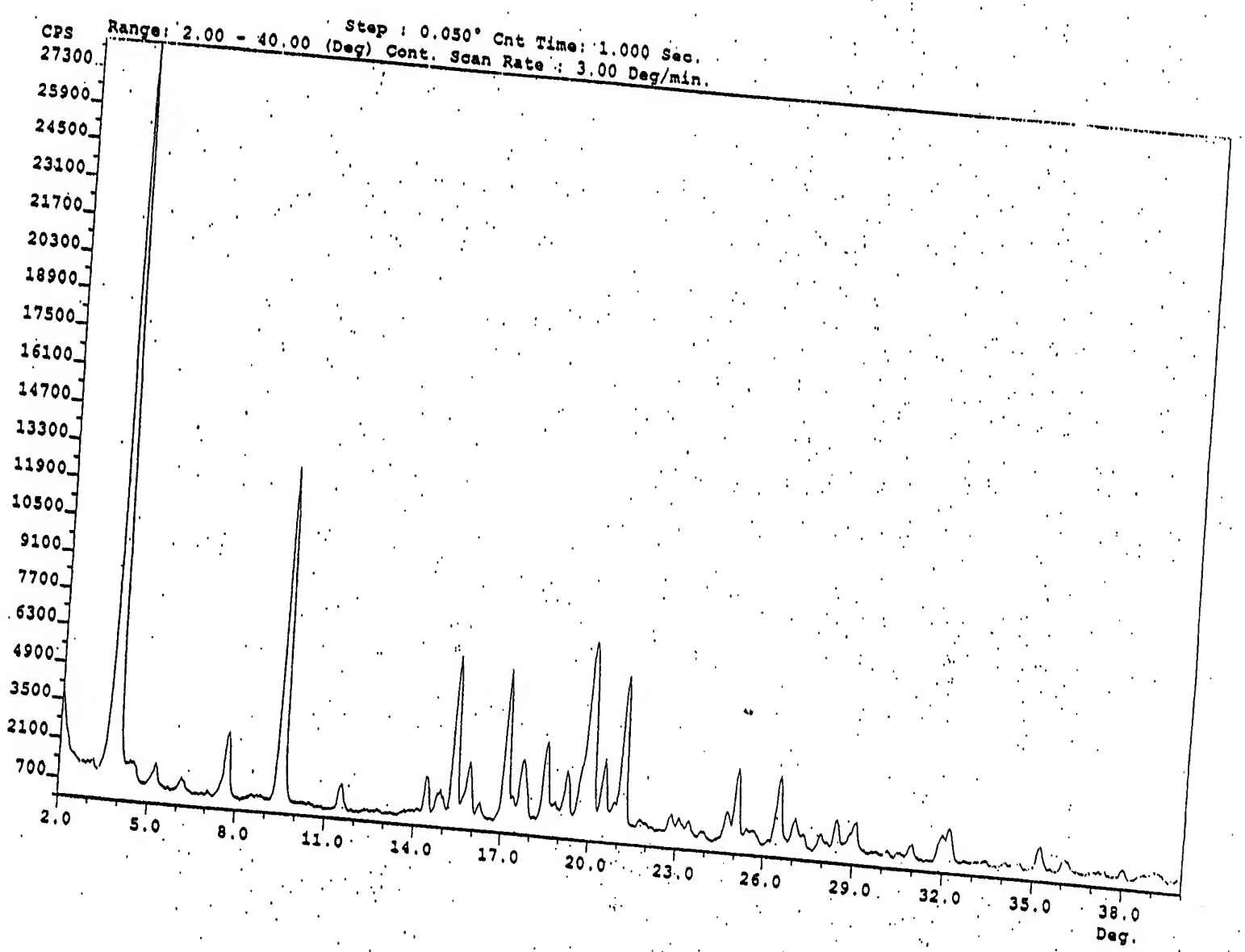

CPS
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
Step : 0.050° Cnt Time: 1.000 Sec.
27300
25900
24500
23100
21700
20300
18900
17500
16100
14700
13300
11900
10500
9100
7700
6300
4900
3500
2100
700
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 10

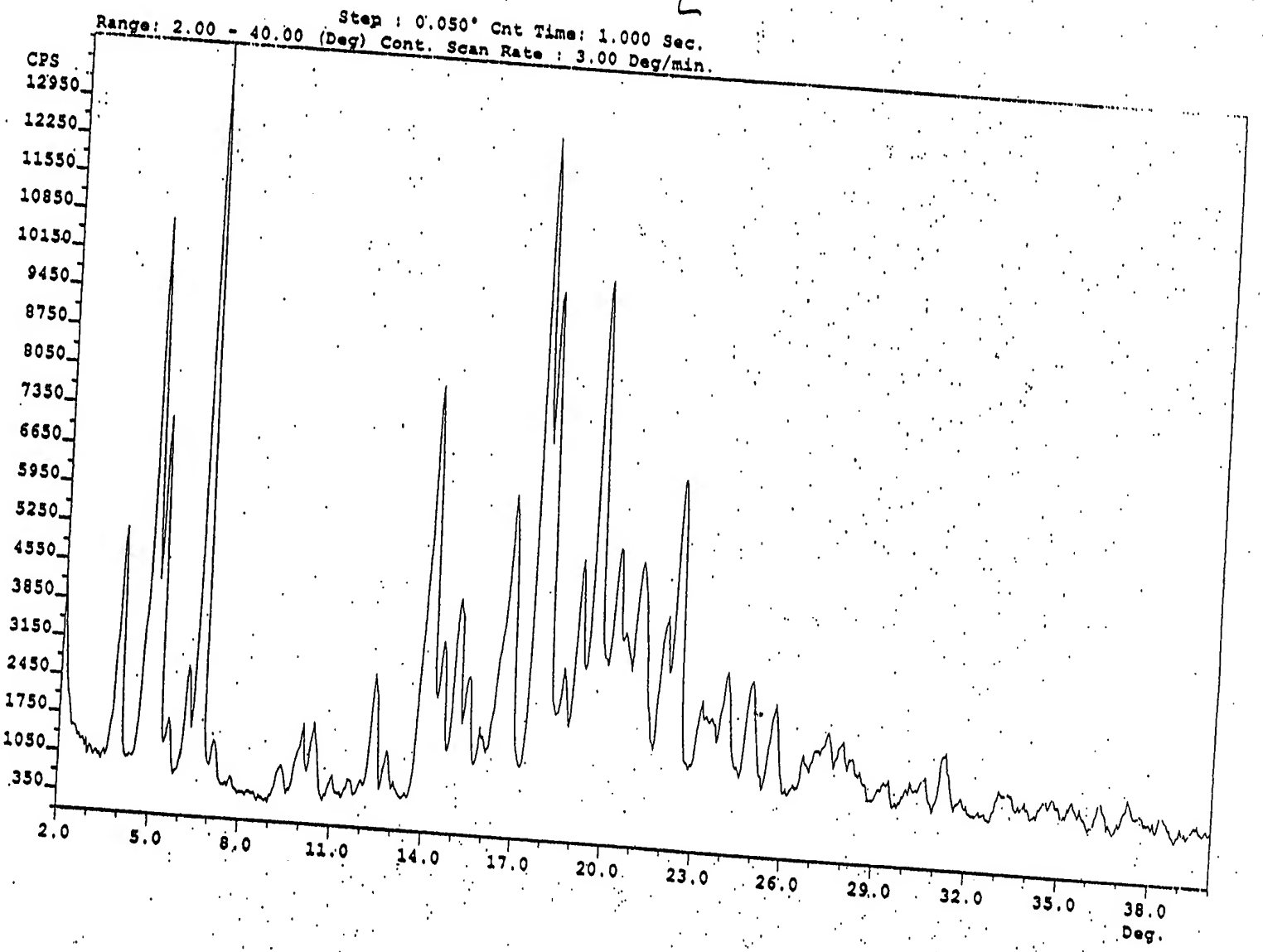

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
CPS
12950
12250
11550
10850
10150
9450
8750
8050
7350
6650
5950
5250
4550
3850
3150
2450
1750
1050
350
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 11

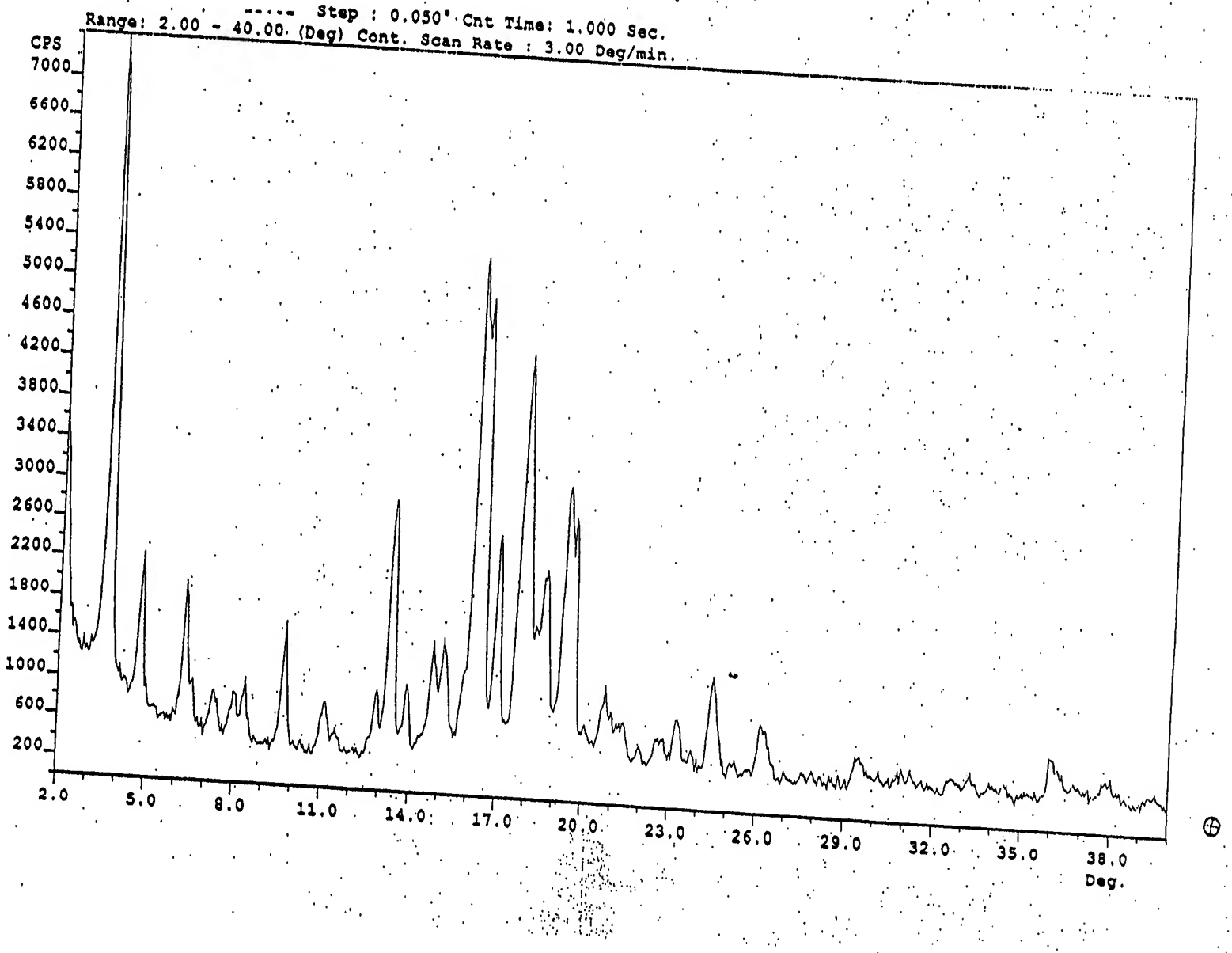

Range: 2.00 - 40.00 (Deg) Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
7000
6600
6200
5800
5400
5000
4600
4200
3800
3400
3000
2600
2200
1800
1400
1000
600
200
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 12

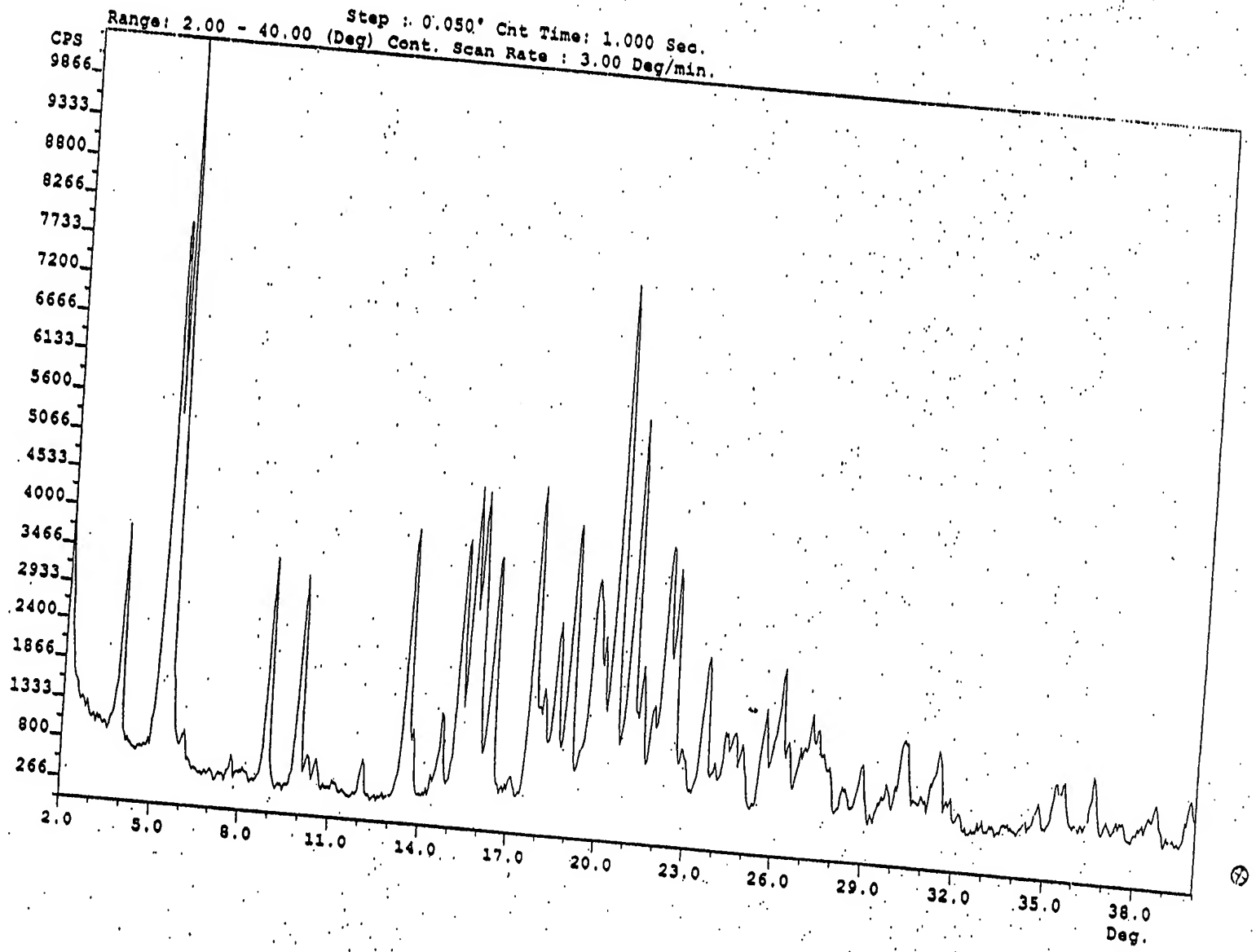

Range: 2.00 - 40.00 (Deg) Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
9866
9333
8800
8266
7733
7200
6666
6133
5600
5066
4533
4000
3466
2933
2400
1866
1333
800
266
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 13

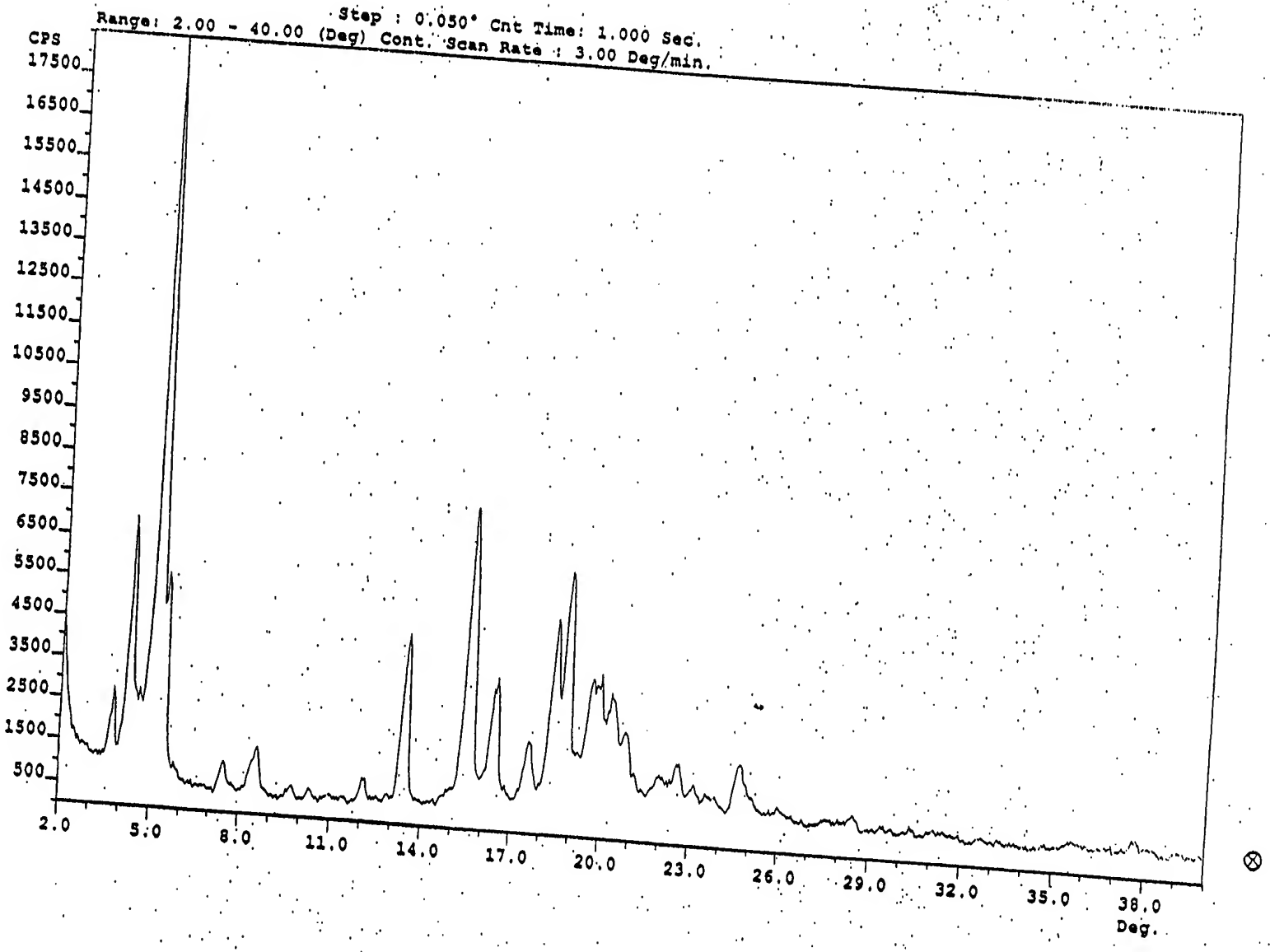

Range: 2.00 - 40.00 (Deg) Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
17500
16500
15500
14500
13500
12500
11500
10500
9500
8500
7500
6500
5500
4500
3500
2500
1500
500
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

fig. 14

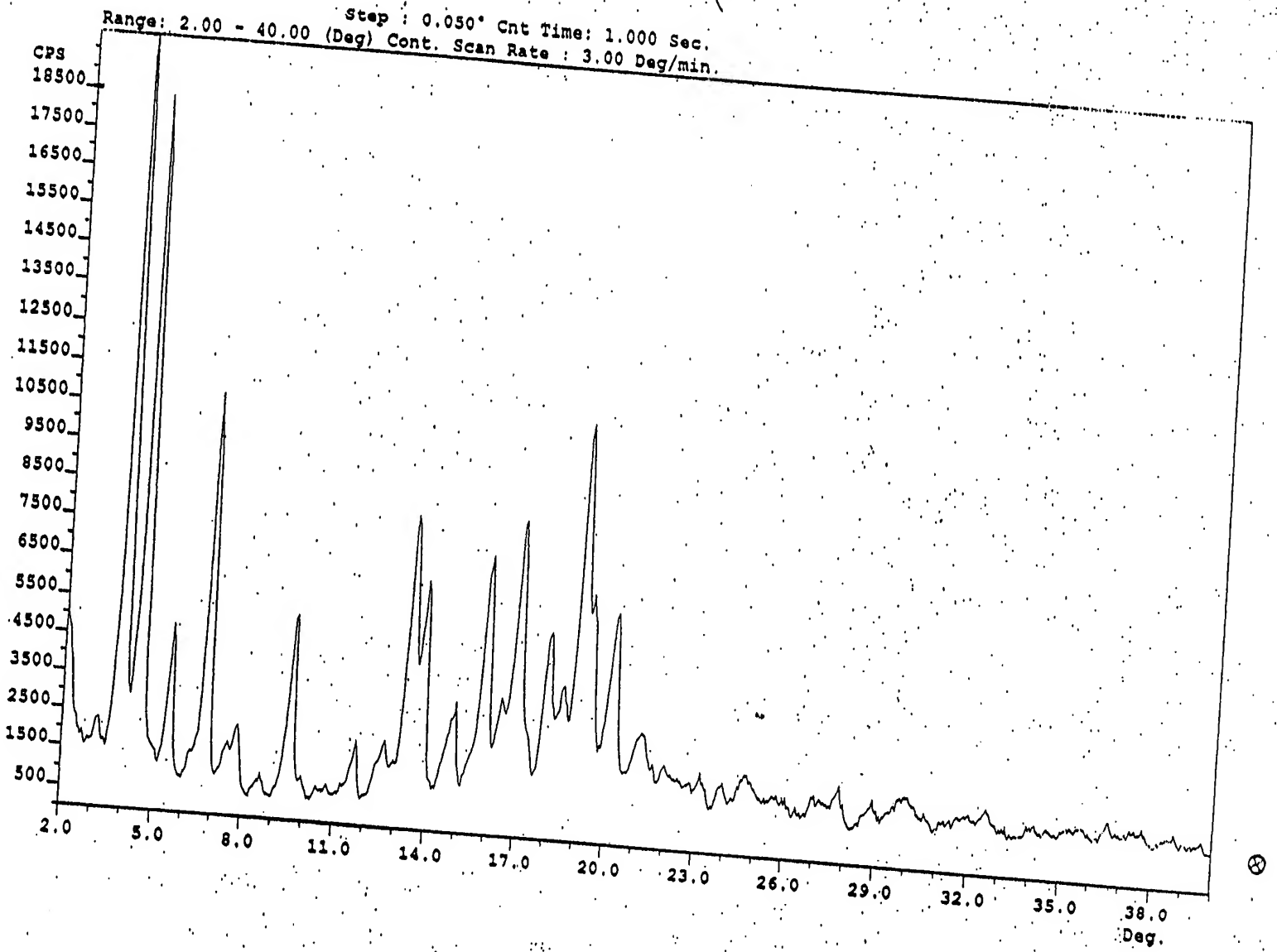

Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
Step : 0.050° Cnt Time: 1.000 Sec.
CPS
18500
17500
16500
15500
14500
13500
12500
11500
10500
9500
8500
7500
6500
5500
4500
3500
2500
1500
500
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 15

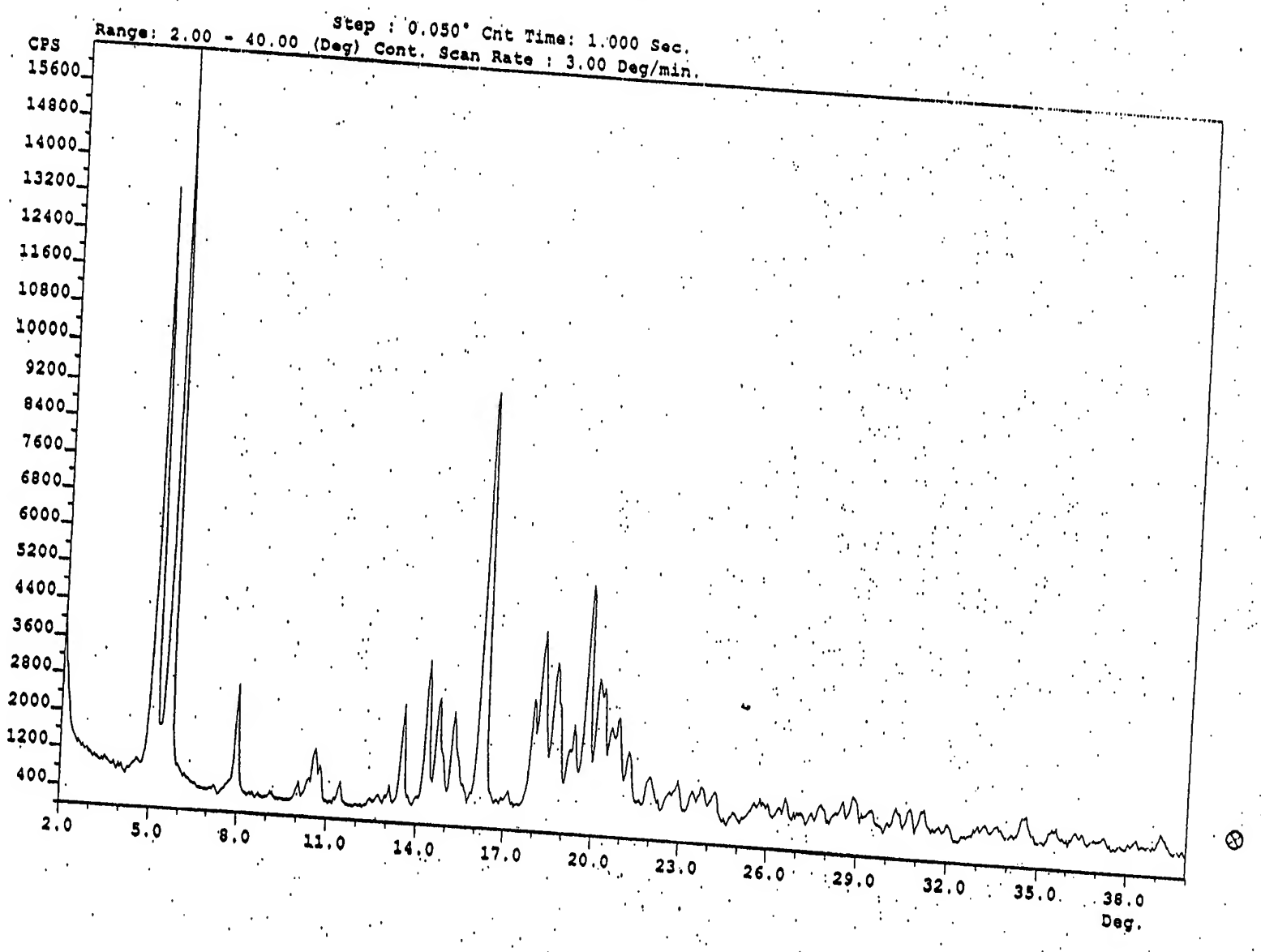

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
CPS
15600
14800
14000
13200
12400
11600
10800
10000
9200
8400
7600
6800
6000
5200
4400
3600
2800
2000
1200
400
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 16

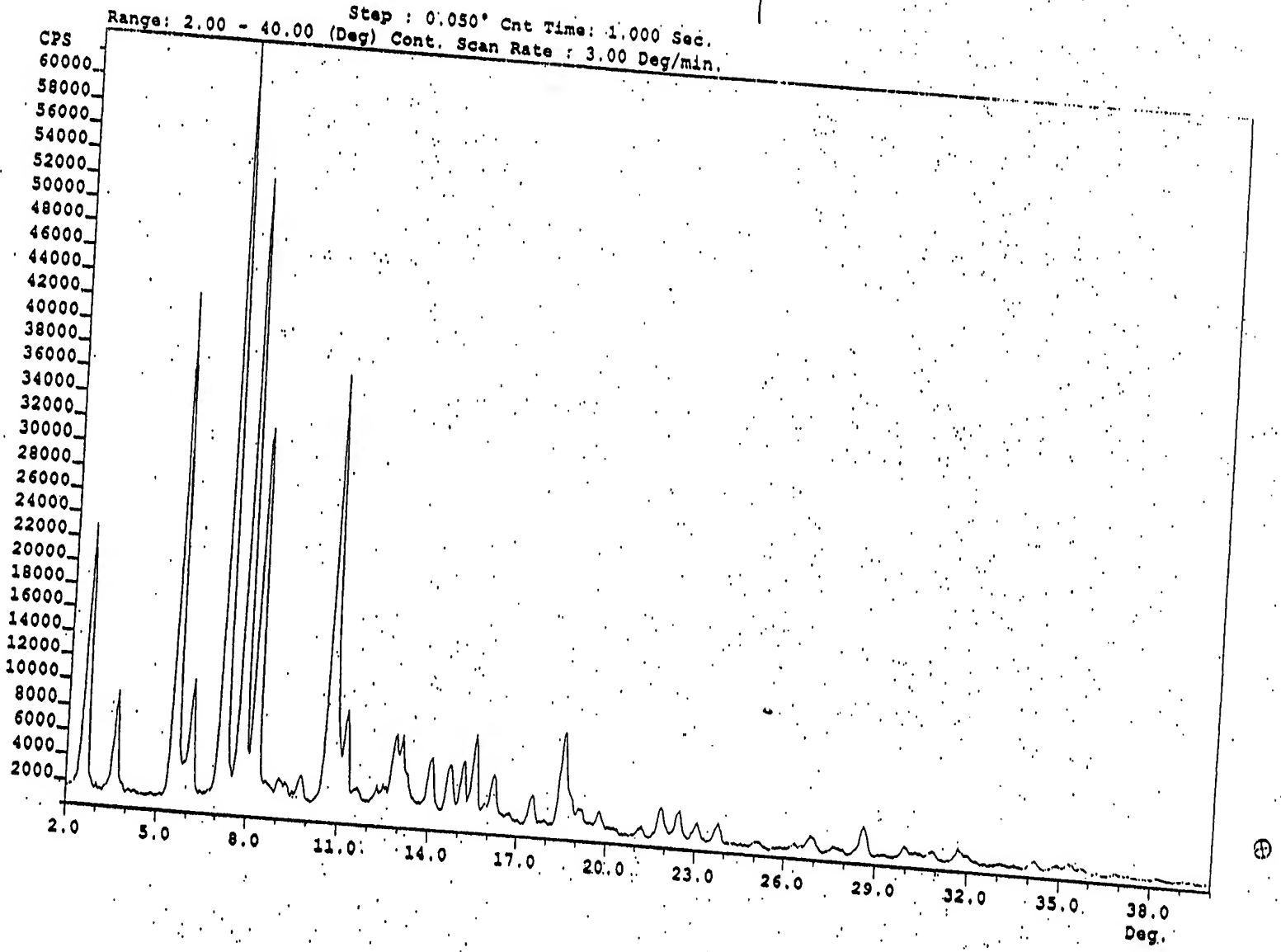

Range: 2.00 - 40.00 (Deg) Step : 0.050° Cnt Time: 1.000 Sec.
Cont. Scan Rate : 3.00 Deg/min.
CPS
60000
58000
56000
54000
52000
50000
48000
46000
44000
42000
40000
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 17. 4

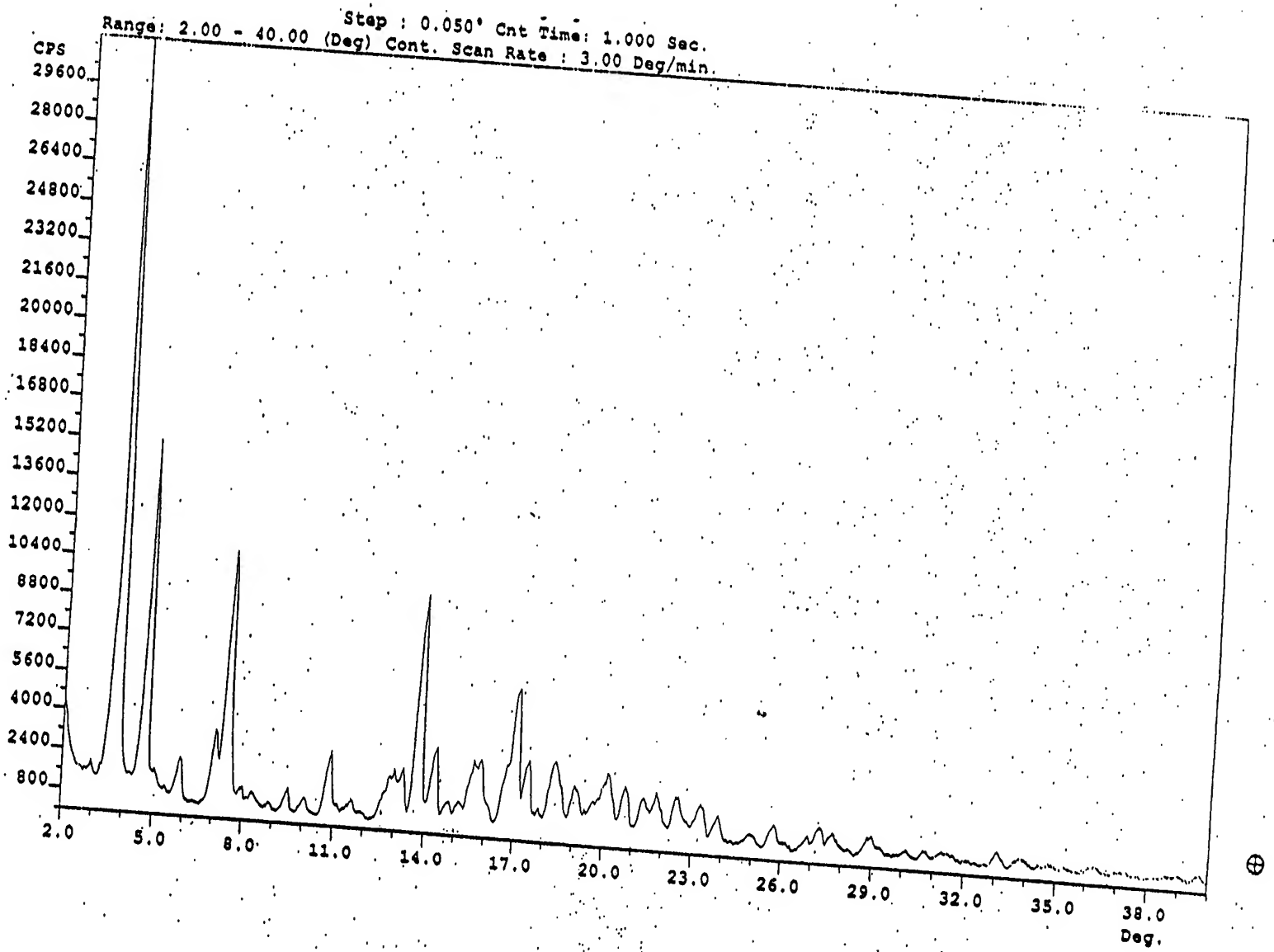

Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
Step : 0.050° Cnt Time: 1.000 Sec.
CPS
29600
28000
26400
24800
23200
21600
20000
18400
16800
15200
13600
12000
10400
8800
7200
5600
4000
2400
800
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 18

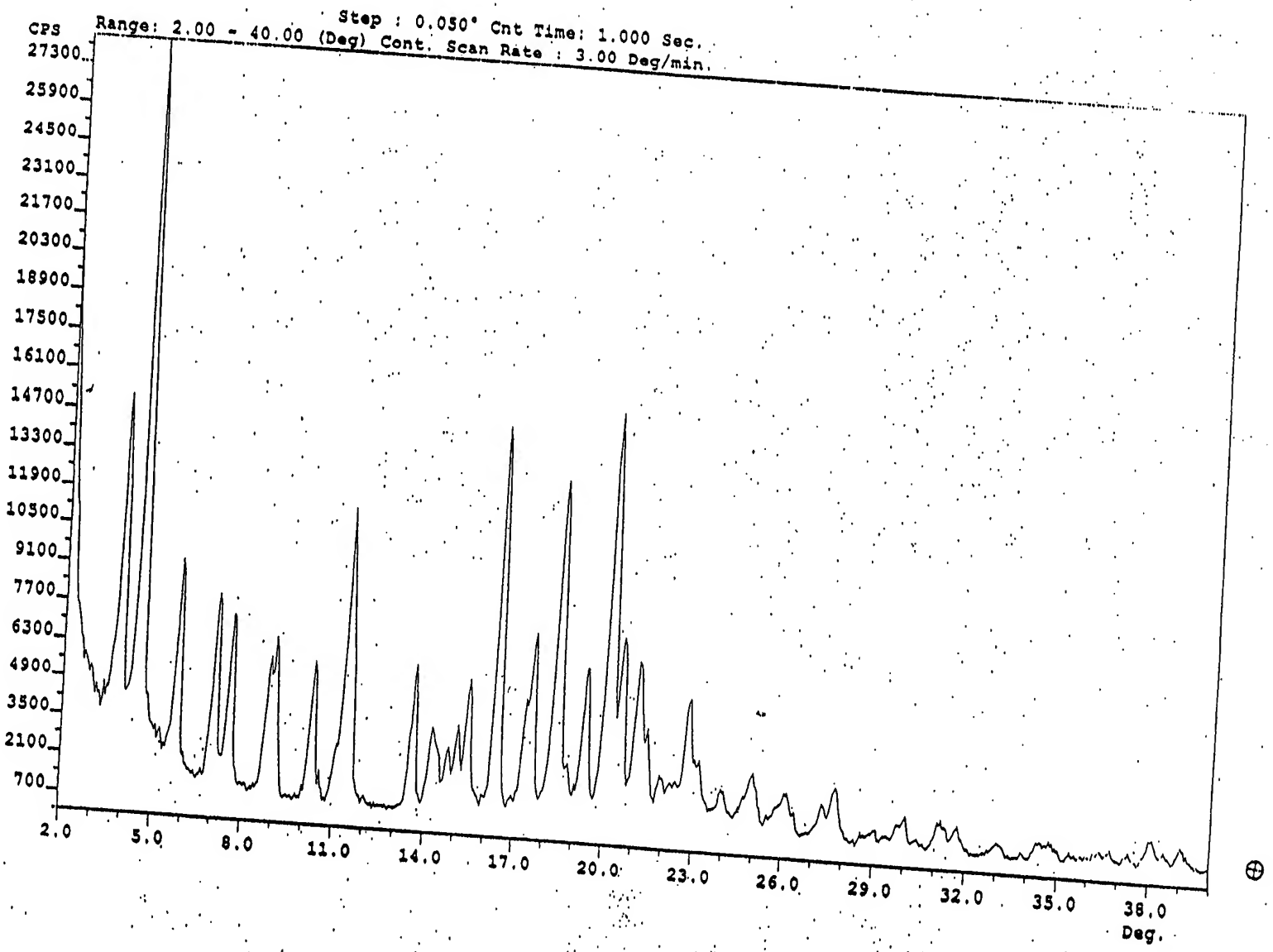

Step : 0.050° Cnt Time: 1.000 Sec.
CPS Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
27300
25900
24500
23100
21700
20300
18900
17500
16100
14700
13300
11900
10500
9100
7700
6300
4900
3500
2100
700
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

fig 19

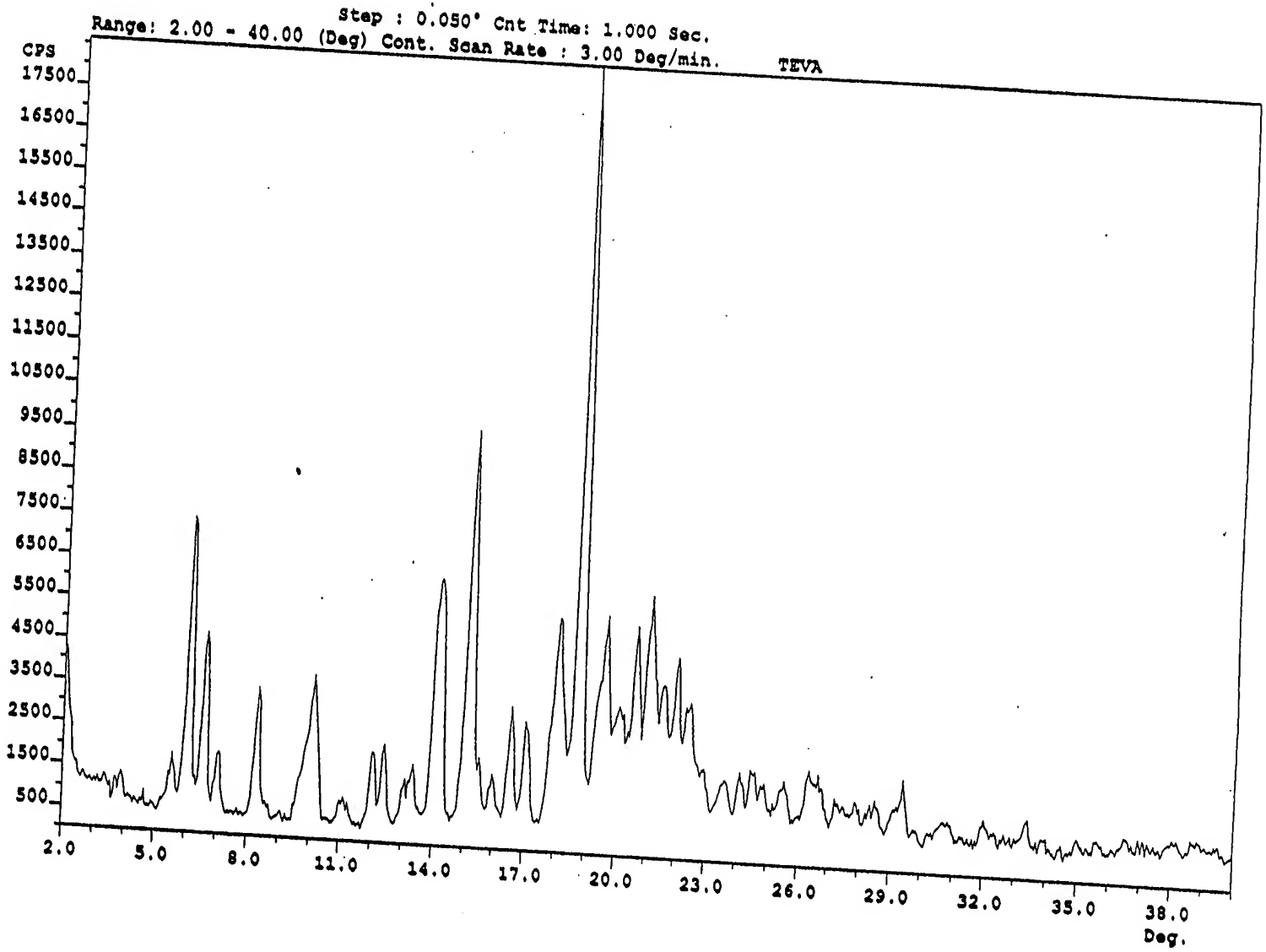

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
17500
16500
15500
14500
13500
12500
11500
10500
9500
8500
7500
6500
5500
4500
3500
2500
1500
500
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Figure 20 - Nateglinide Form Z

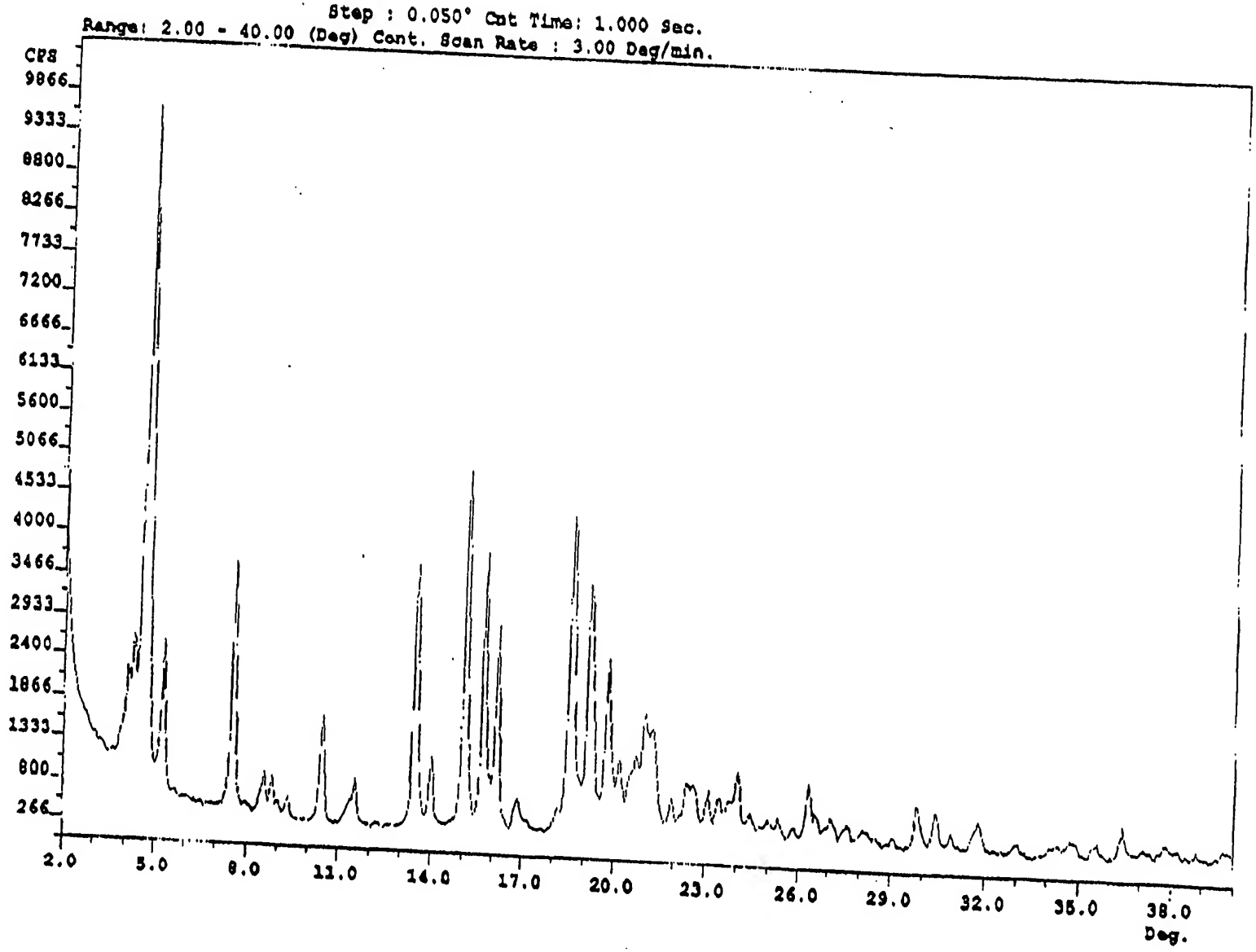


fig 2φ α

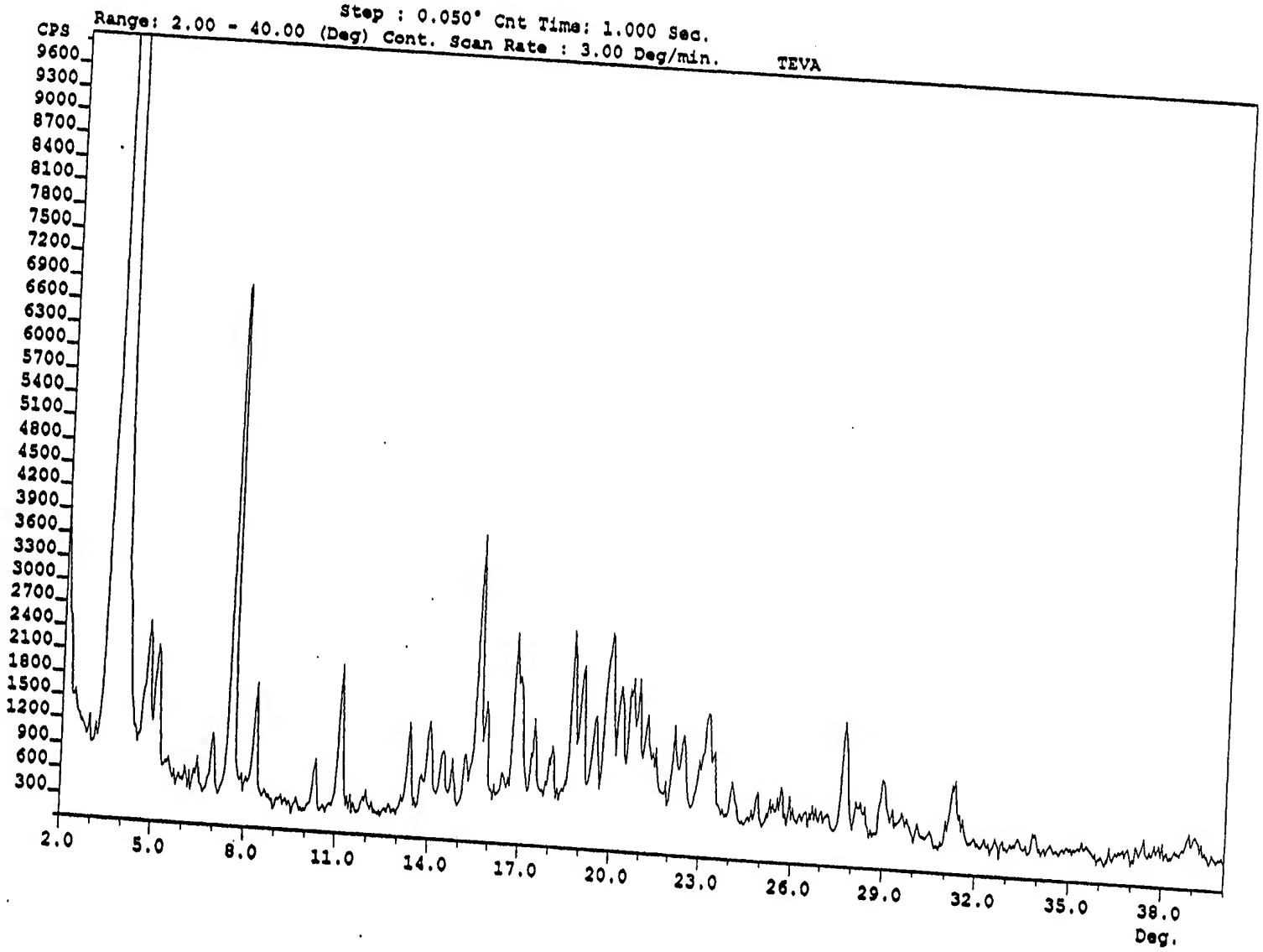

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
9600
9300
9000
8700
8400
8100
7800
7500
7200
6900
6600
6300
6000
5700
5400
5100
4800
4500
4200
3900
3600
3300
3000
2700
2400
2100
1800
1500
1200
900
600
300
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig. 2B

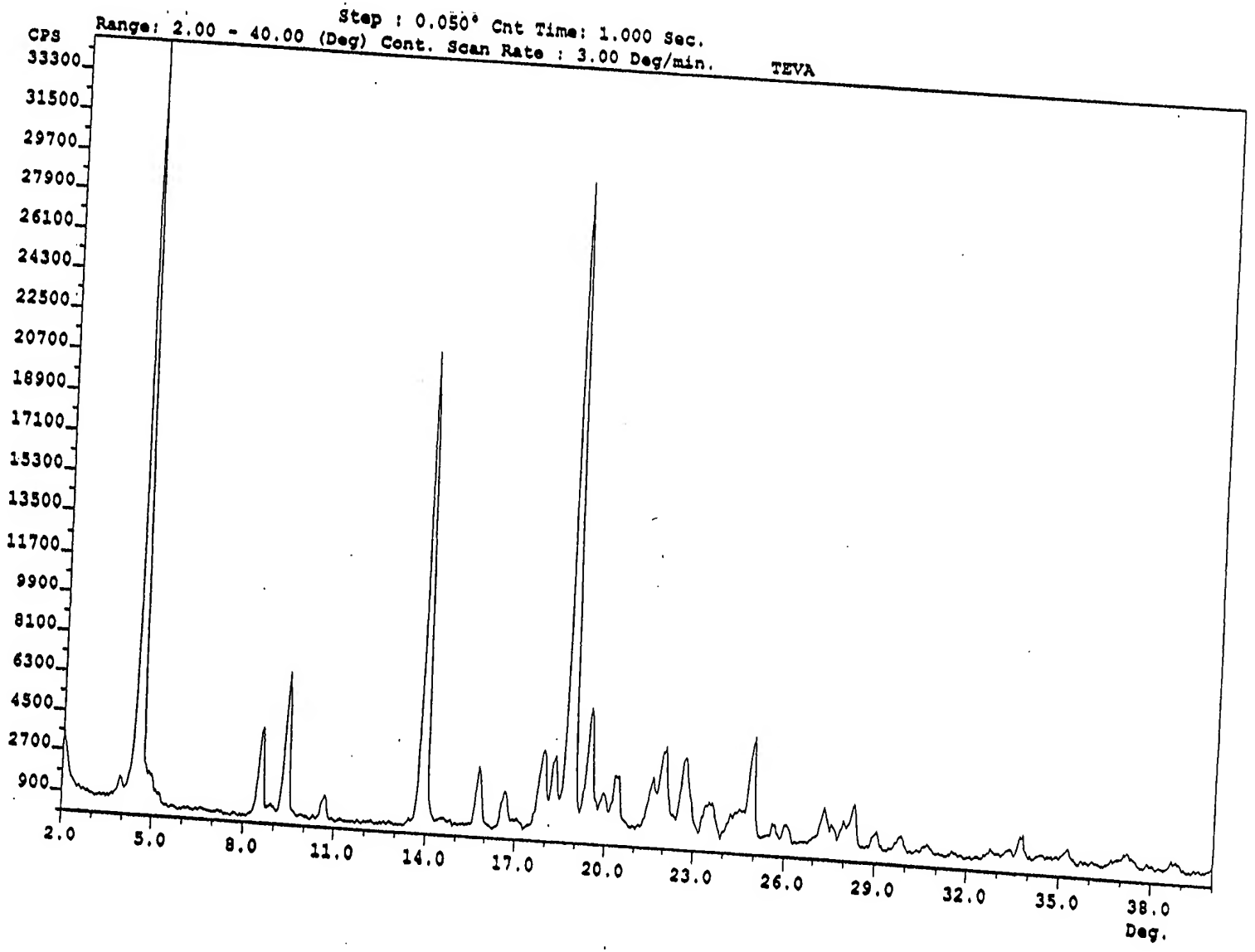

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
33300
31500
29700
27900
26100
24300
22500
20700
18900
17100
15300
13500
11700
9900
8100
6300
4500
2700
900
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig 23 P

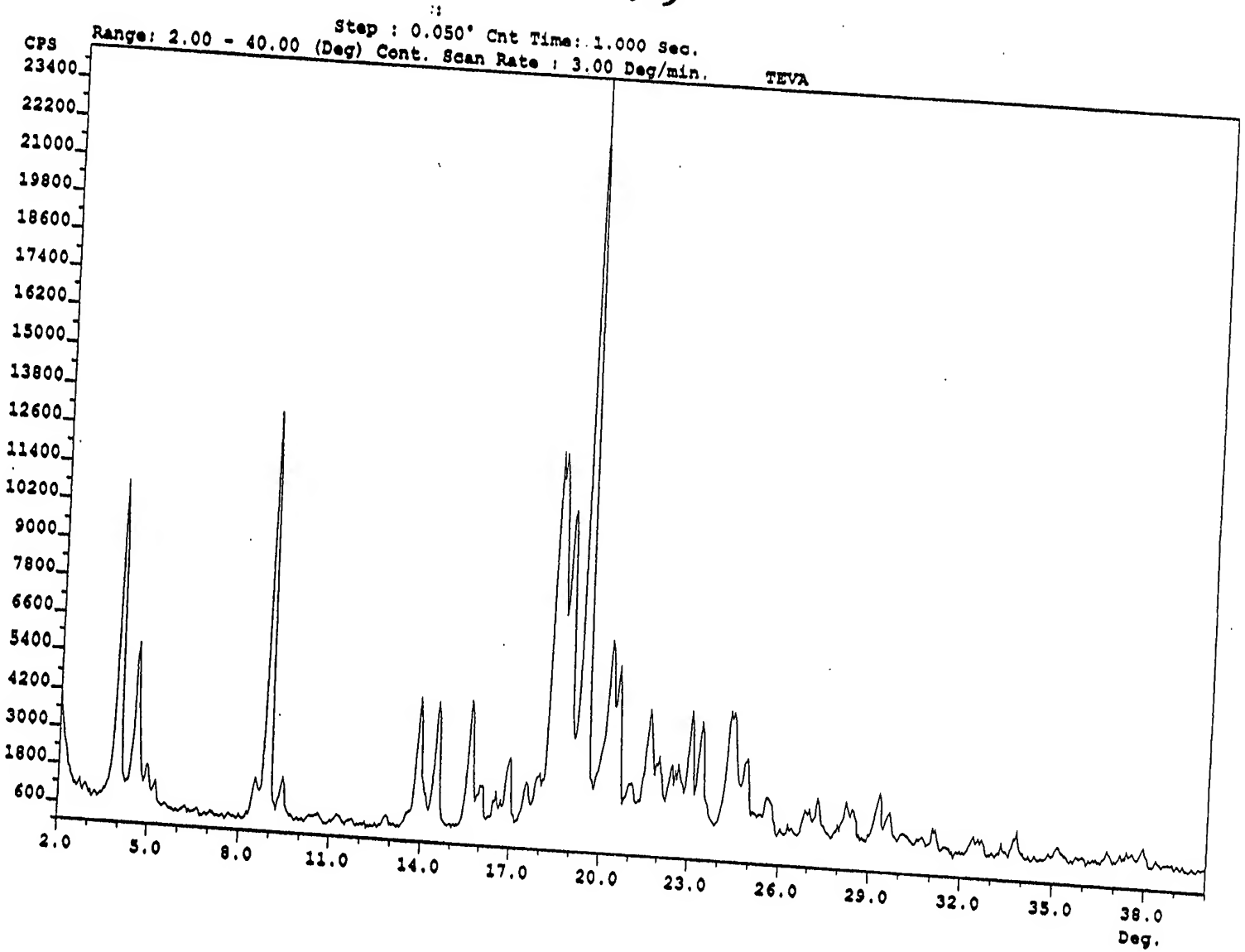

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
23400
22200
21000
19800
18600
17400
16200
15000
13800
12600
11400
10200
9000
7800
6600
5400
4200
3000
1800
600
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig 24 d

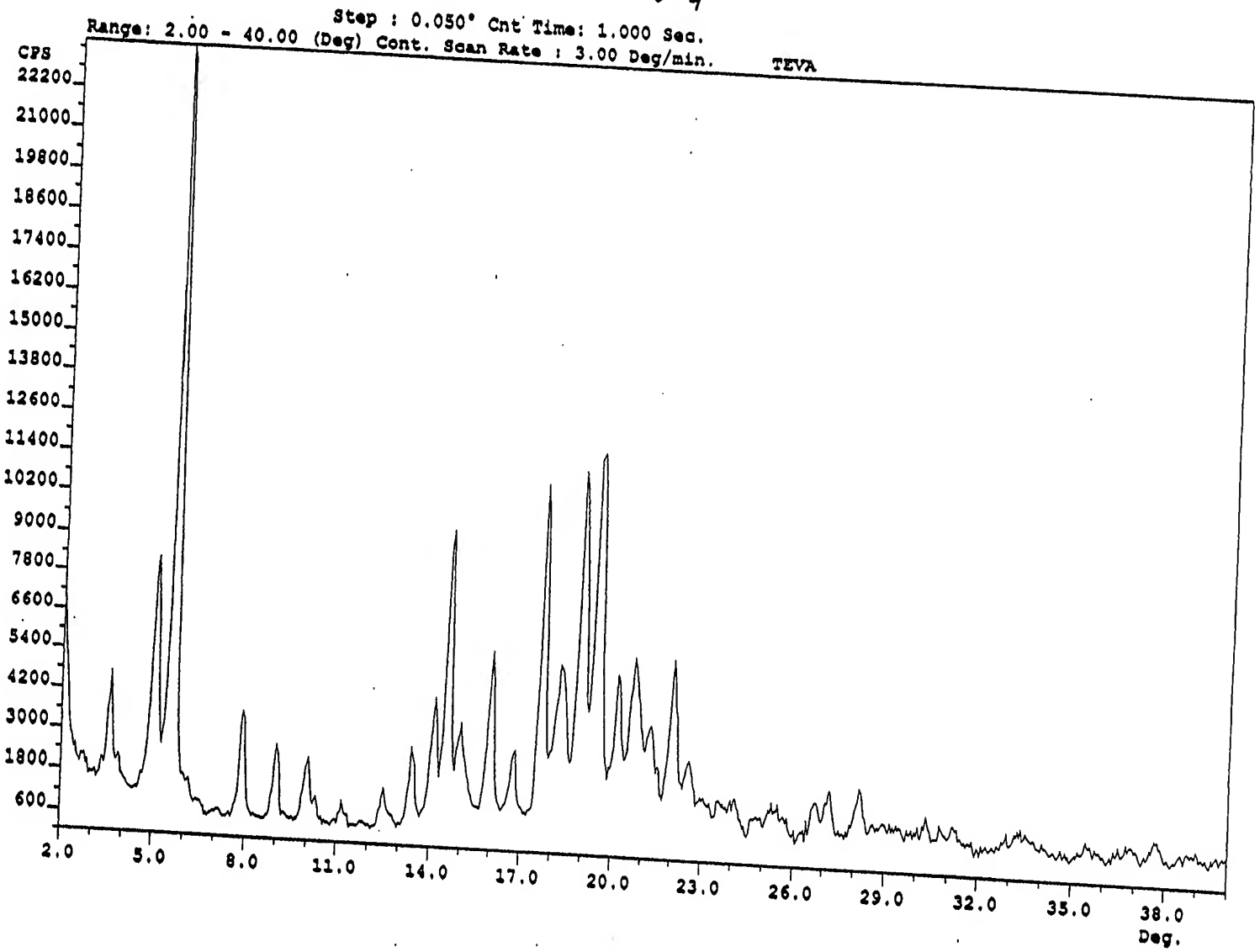

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
22200
21000
19800
18600
17400
16200
15000
13800
12600
11400
10200
9000
7800
6600
5400
4200
3000
1800
600
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

Fig 25

E

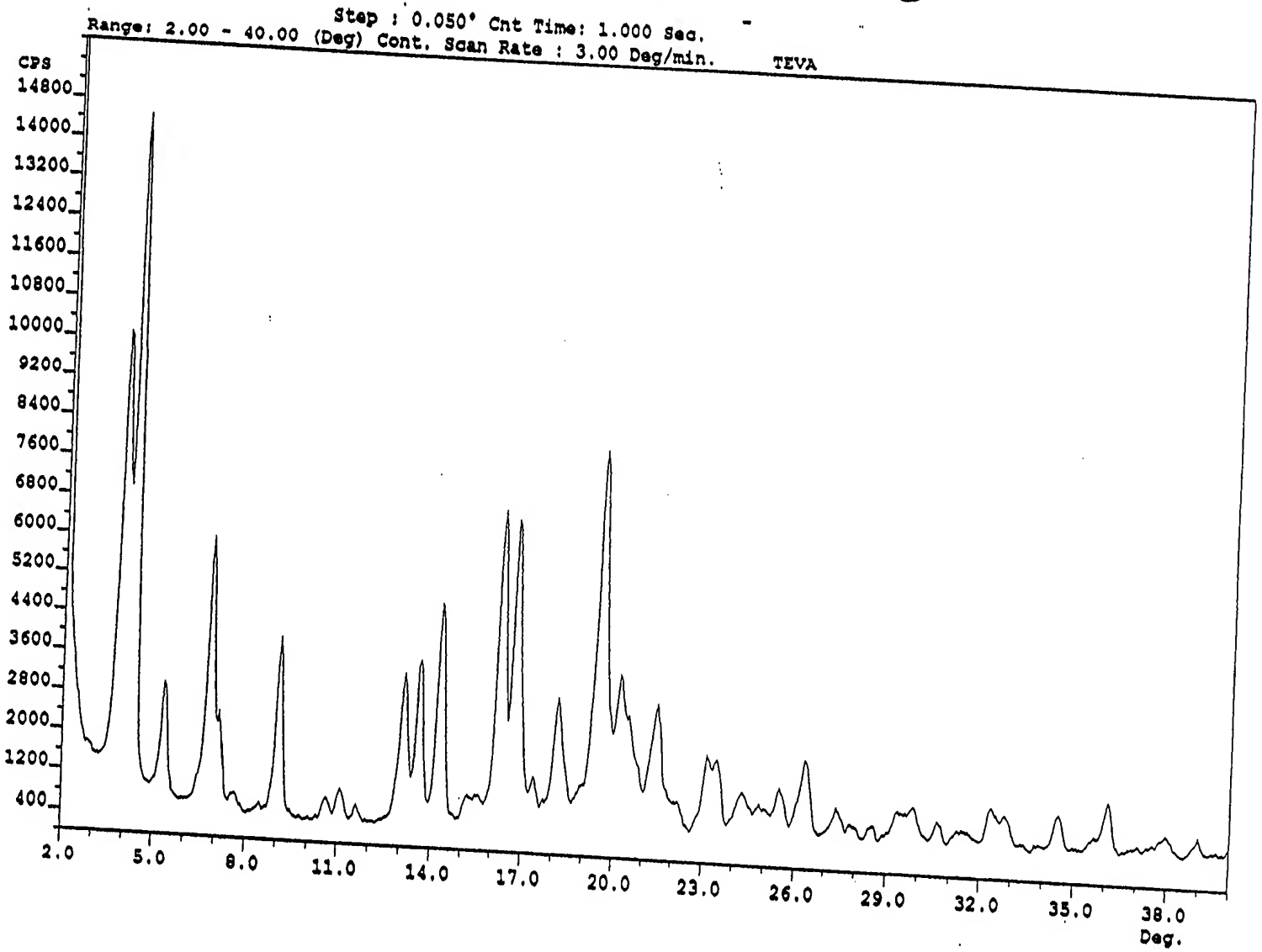
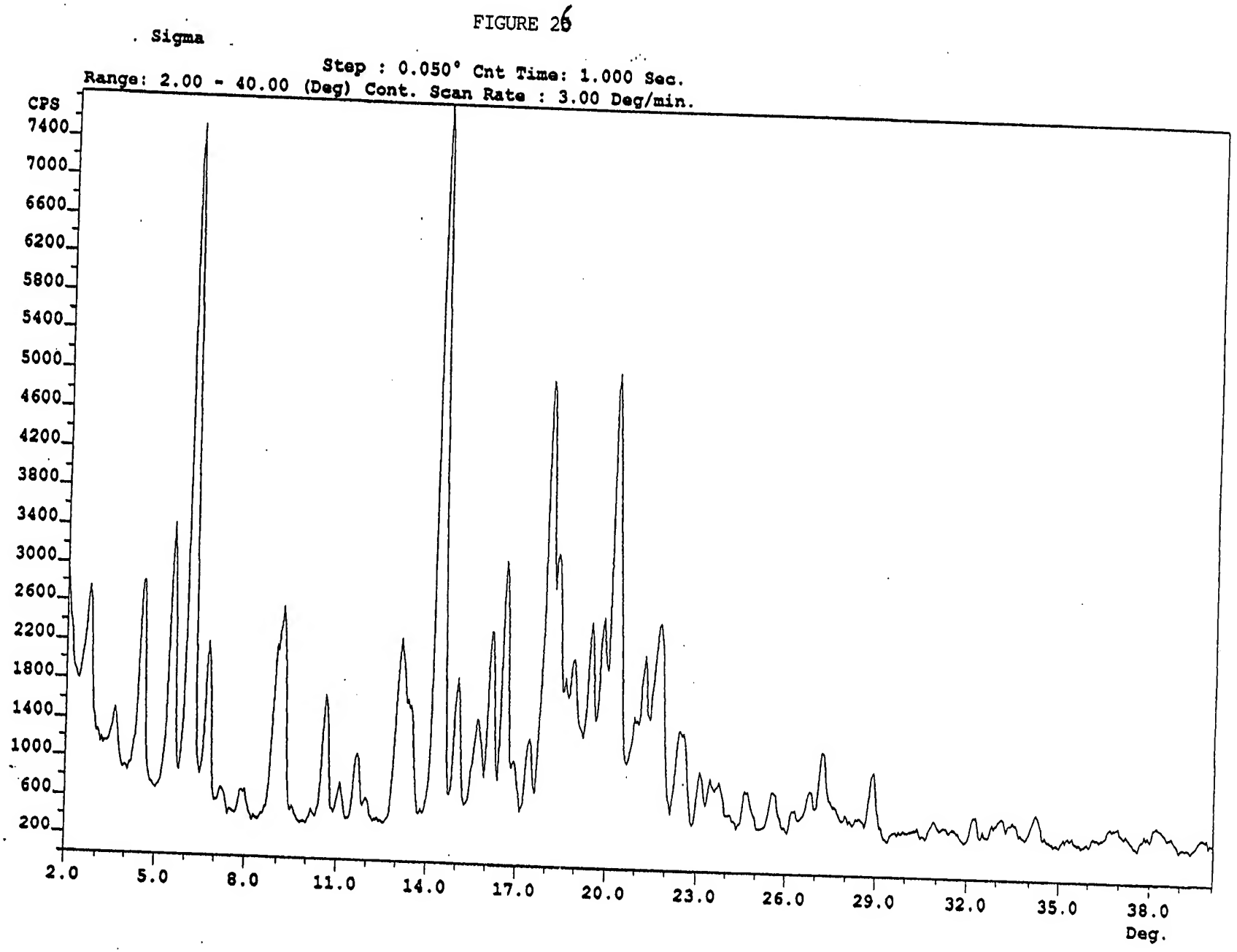
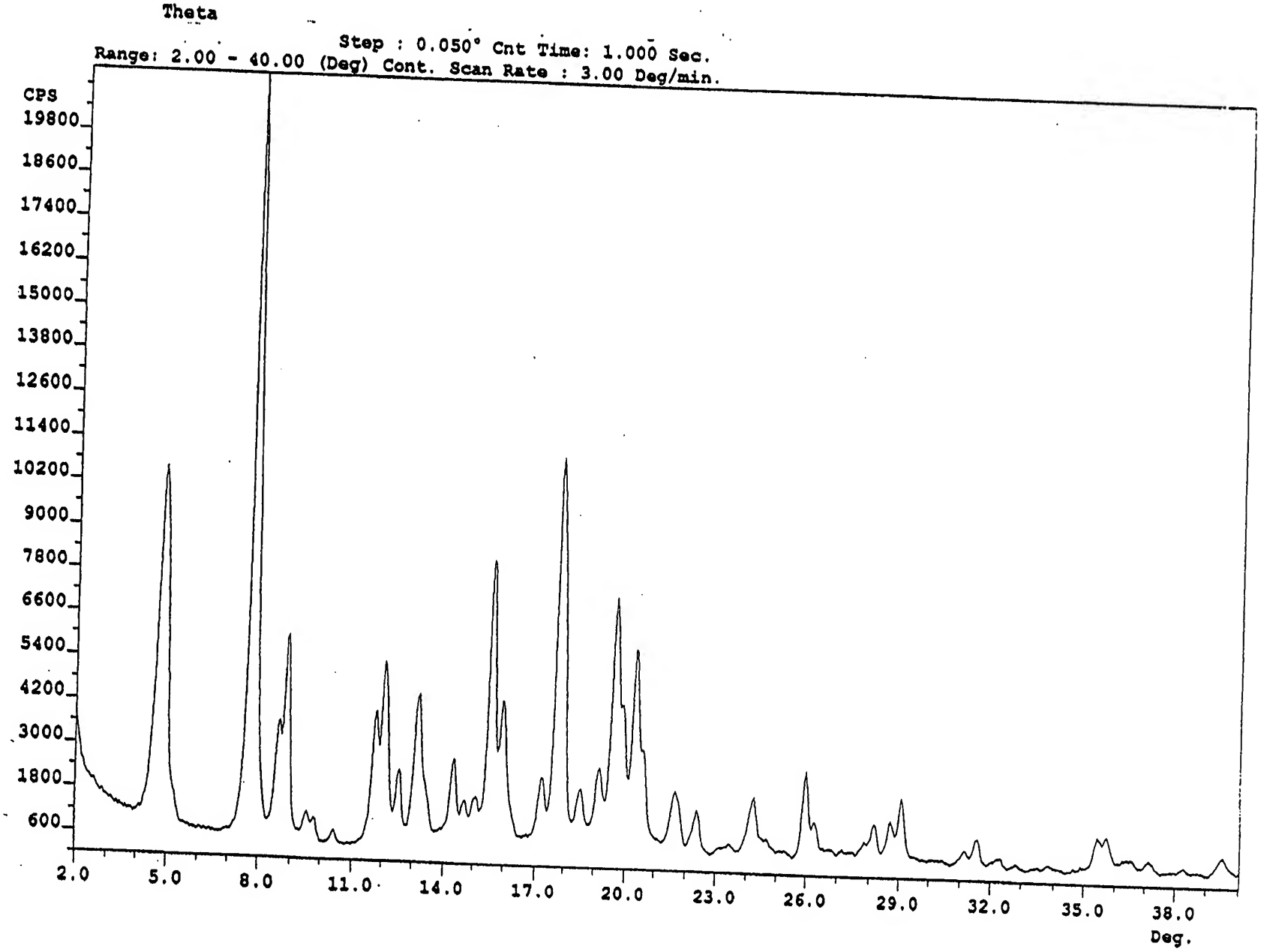

Step : 0.050° Cnt Time: 1.000 Sec.
Range: 2.00 - 40.00 (Deg) Cont. Scan Rate : 3.00 Deg/min.
TEVA
CPS
14800
14000
13200
12400
11600
10800
10000
9200
8400
7600
6800
6000
5200
4400
3600
2800
2000
1200
400
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
32.0
35.0
38.0
Deg.

FIGURE 26



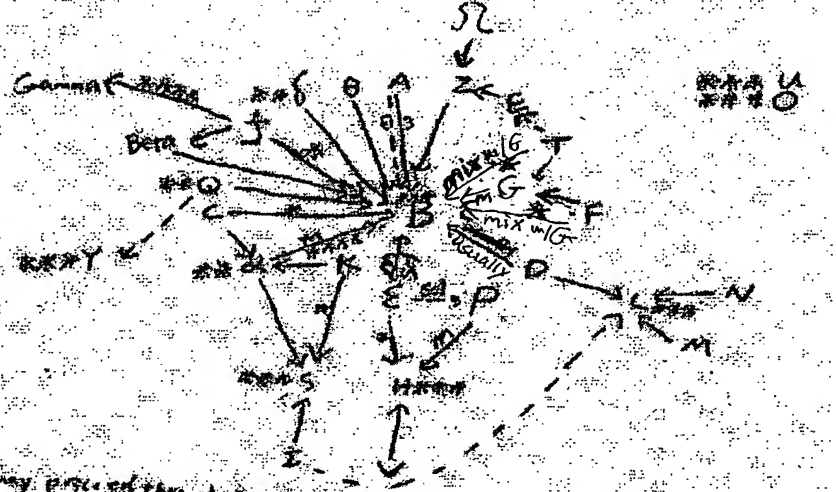

Form α (σ)

FIGURE 27



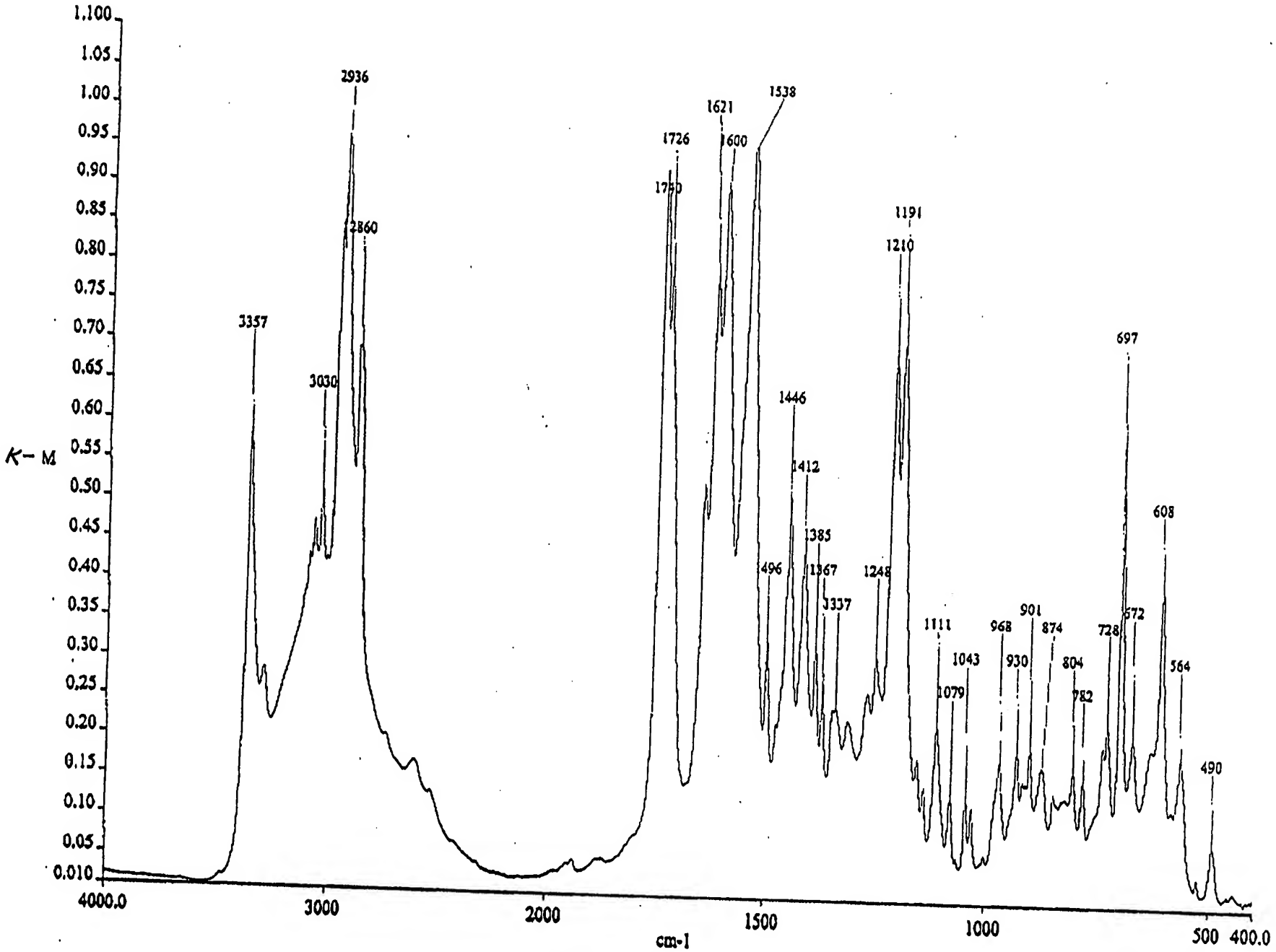

Form α

Figure 28 - Thermal stability chart




* Transformation may proceed through another form
** Thermally stable at lower heating temperatures (~ 50°C)
*** Thermally stable forms
---→ Transformation after storage at room temperature
m Mixture with starting form
xxxx When starting material contains seeds.
sol Results might vary depending on the solvate of Form Epsilon used.

FIGURE 2C
- Form L




- DRIFT,4000-400 CM-1, 16 scans, Resolution:4.00cm-1

FIGURE 30
- Form P

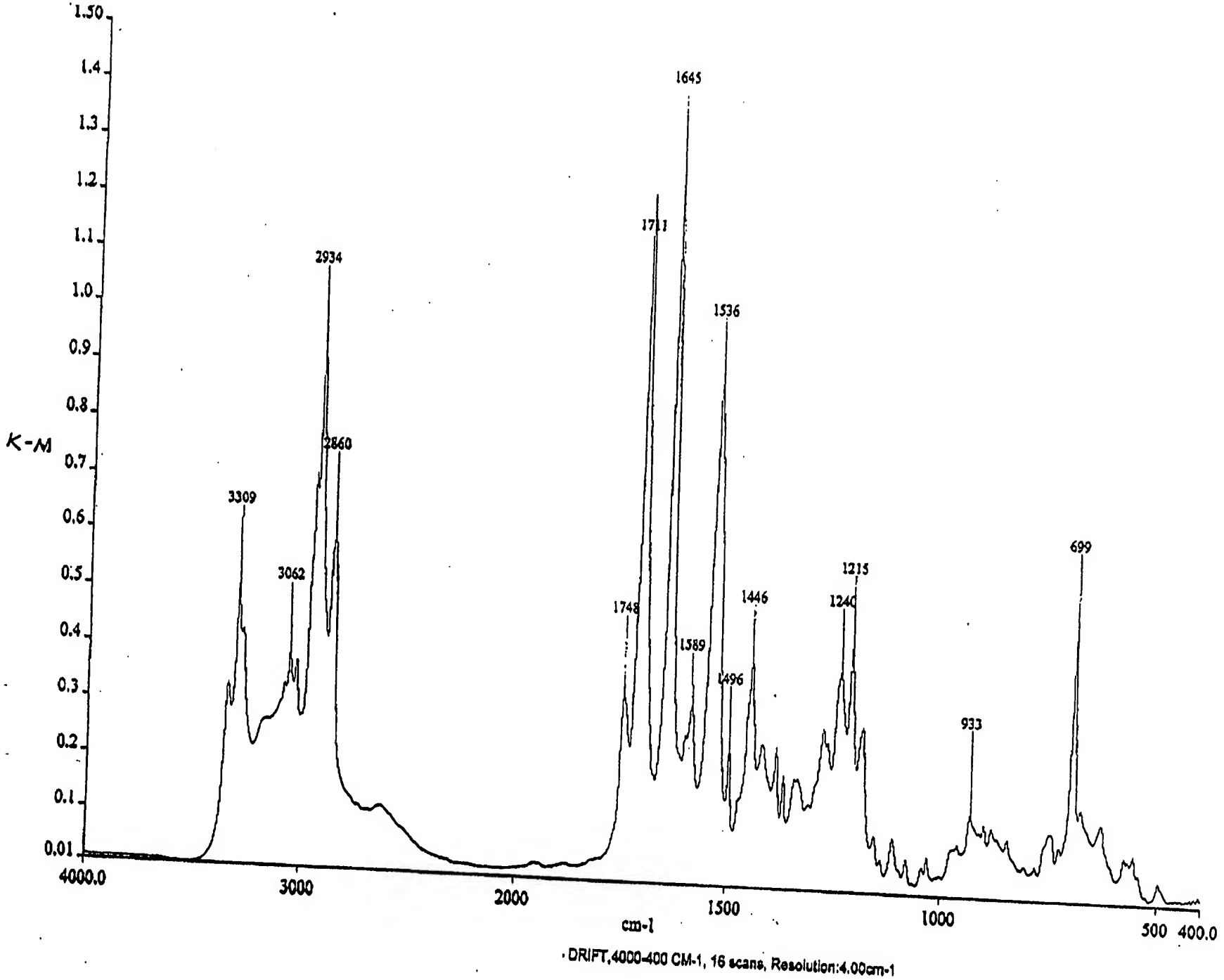
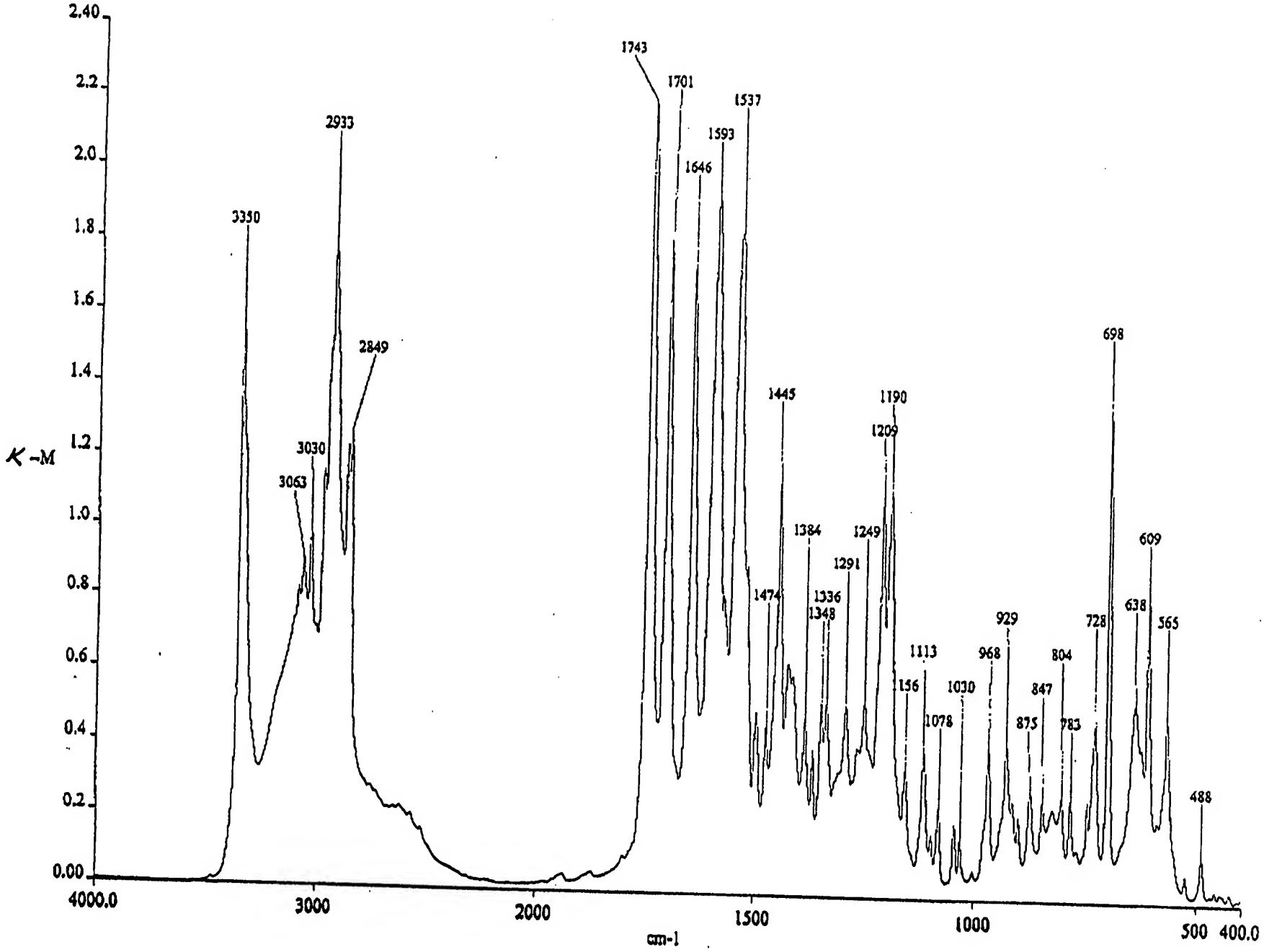


FIGURE 3ϕ
Form U




- DRIFT, 4000-400cm-1, 16 scans, resolution: 4.0cm-1

Figure 32 - Nateglinide Form 2

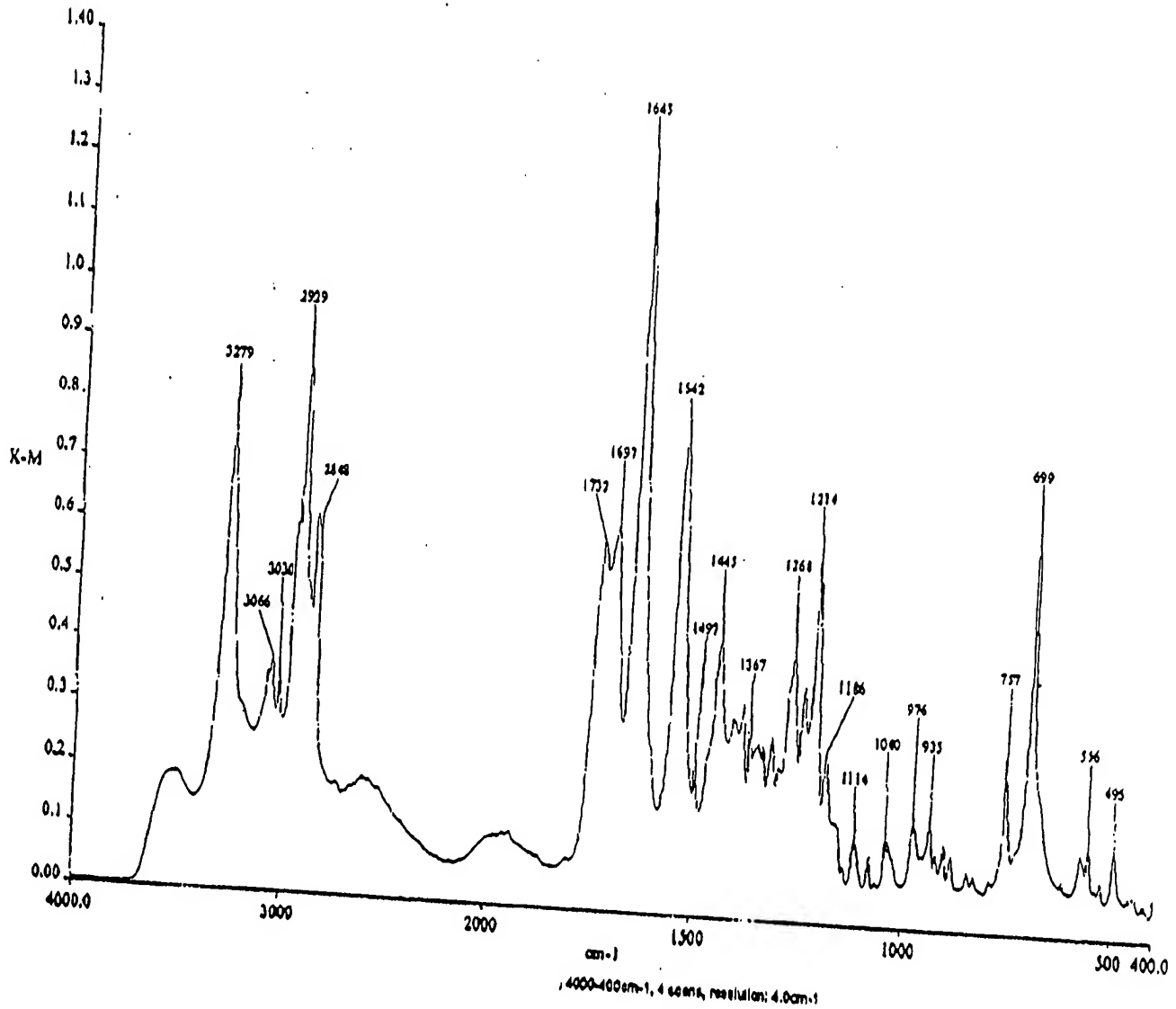


FIGURE 33
Form α

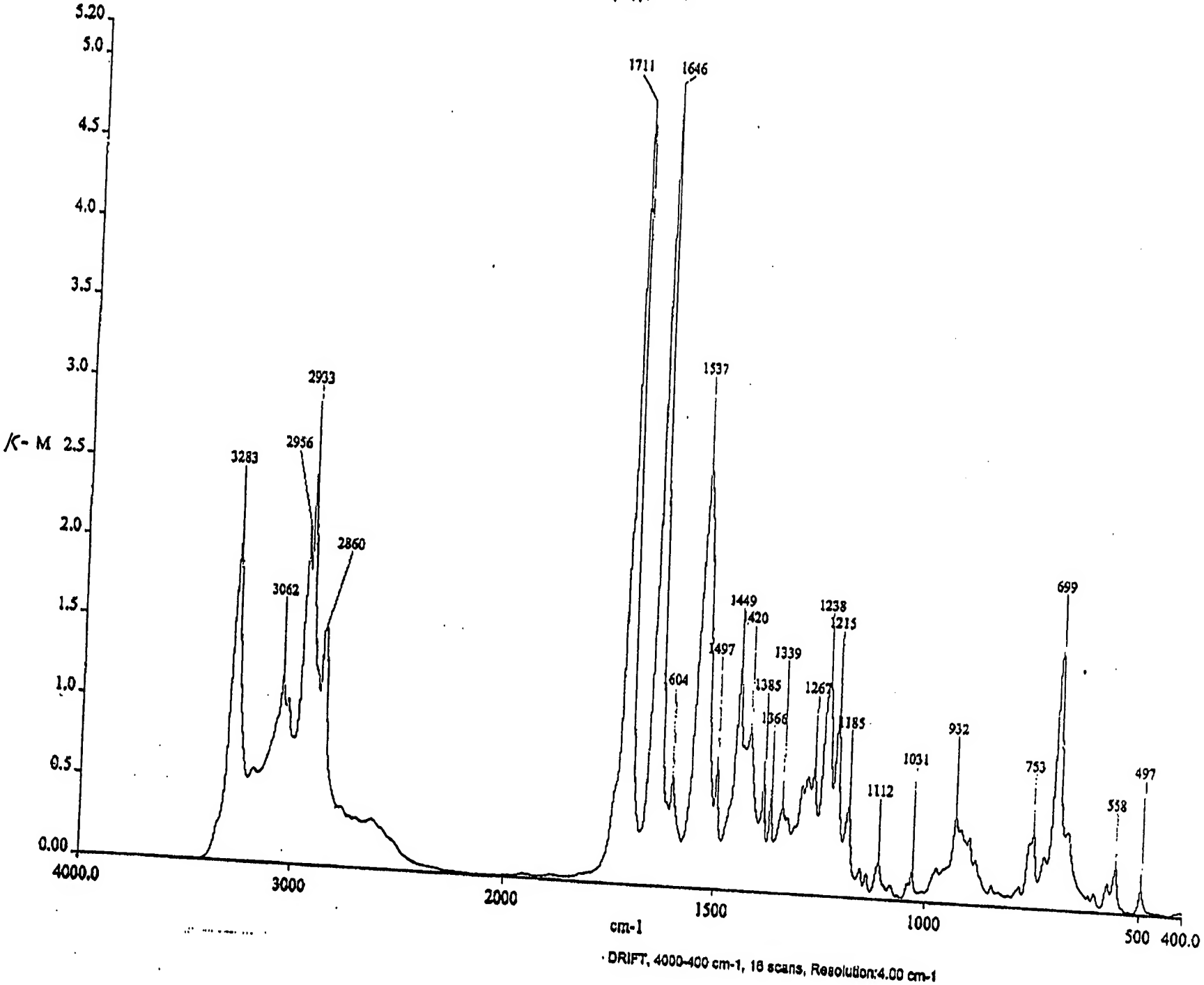


FIGURE 34 From delta

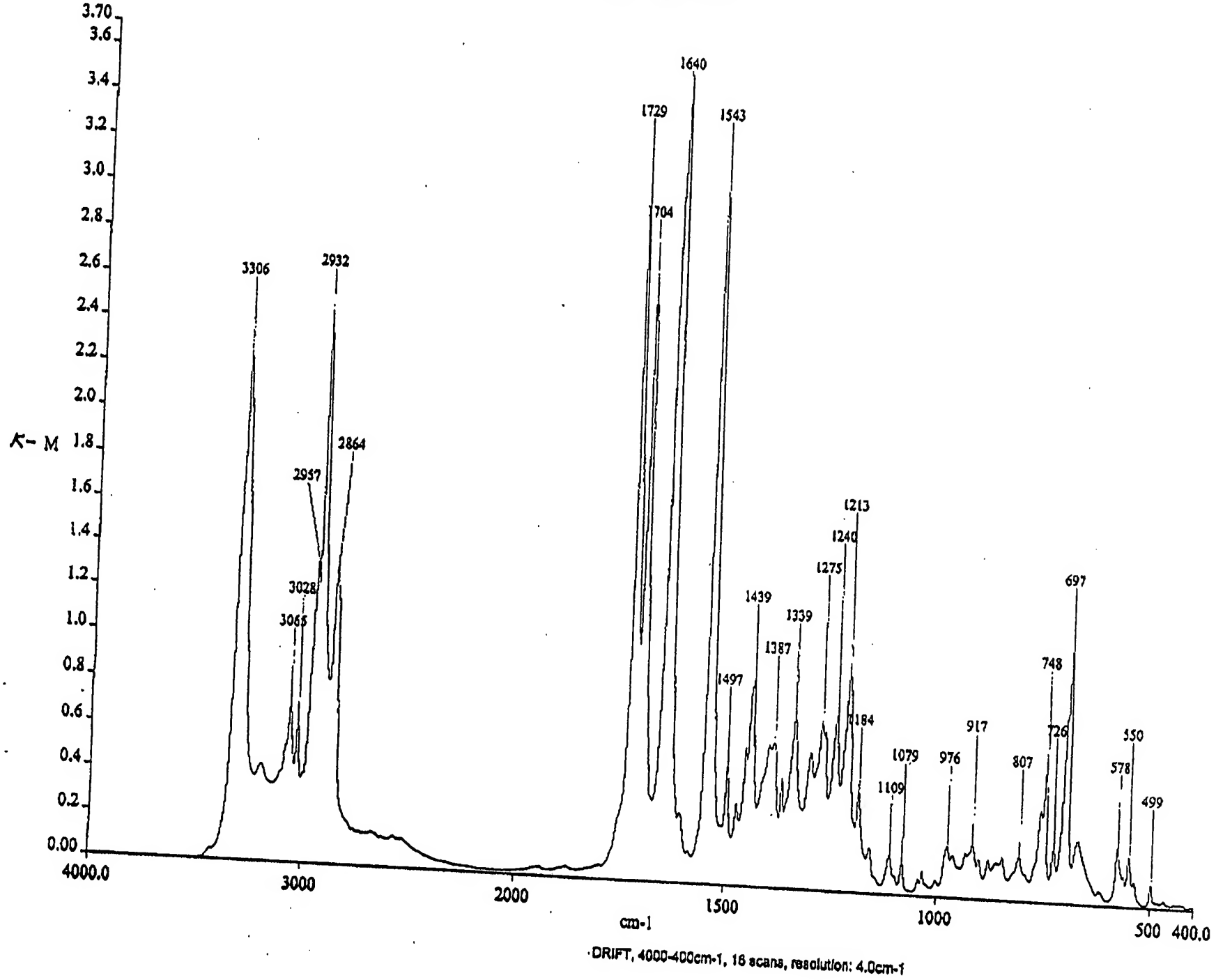
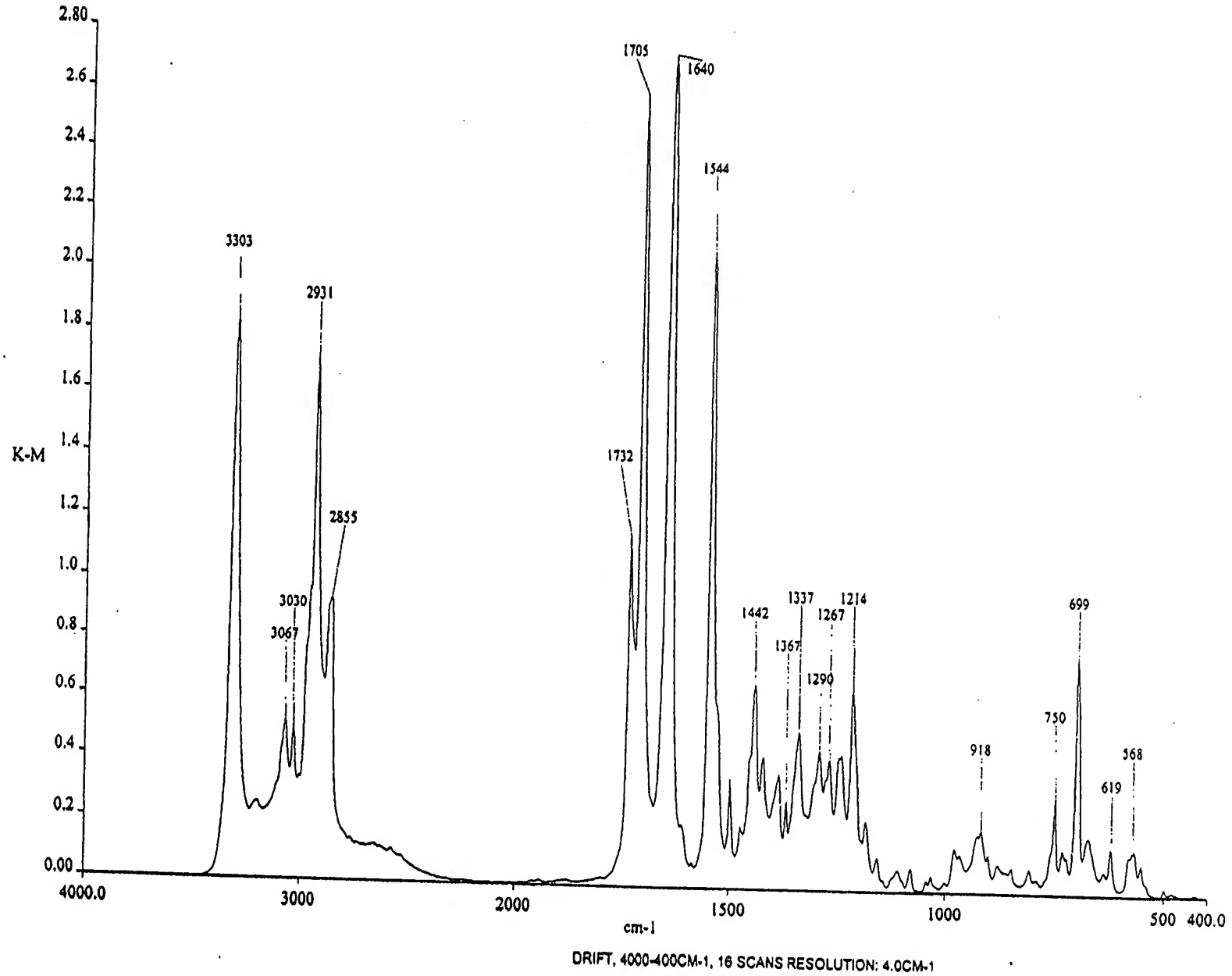


FIGURE 35 - Form O




DRIFT, 4000-400CM-1, 16 SCANS RESOLUTION: 4.0CM-1

form ~ (O)

FIGURE 36

Form A

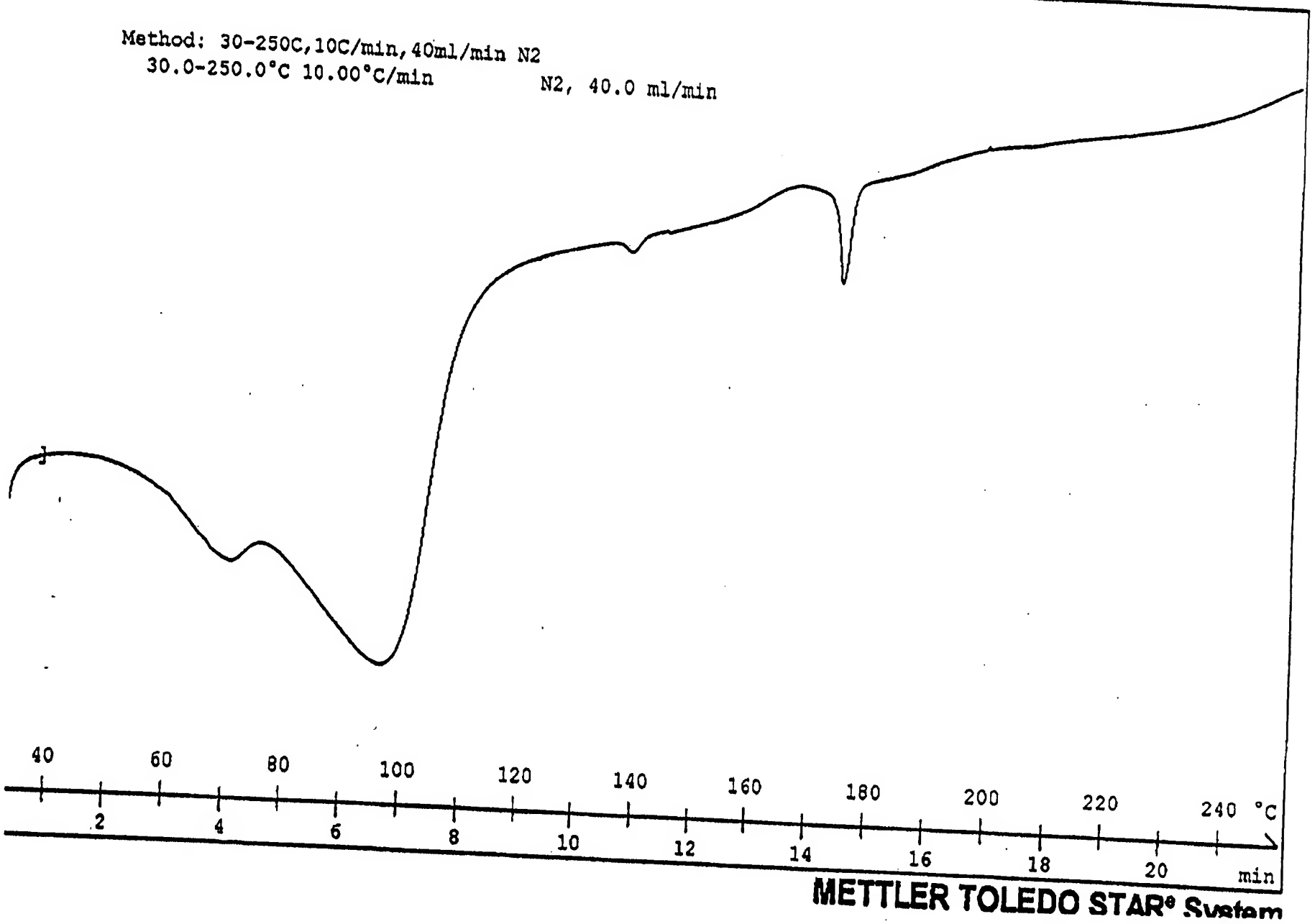


FIGURE 37 Form D

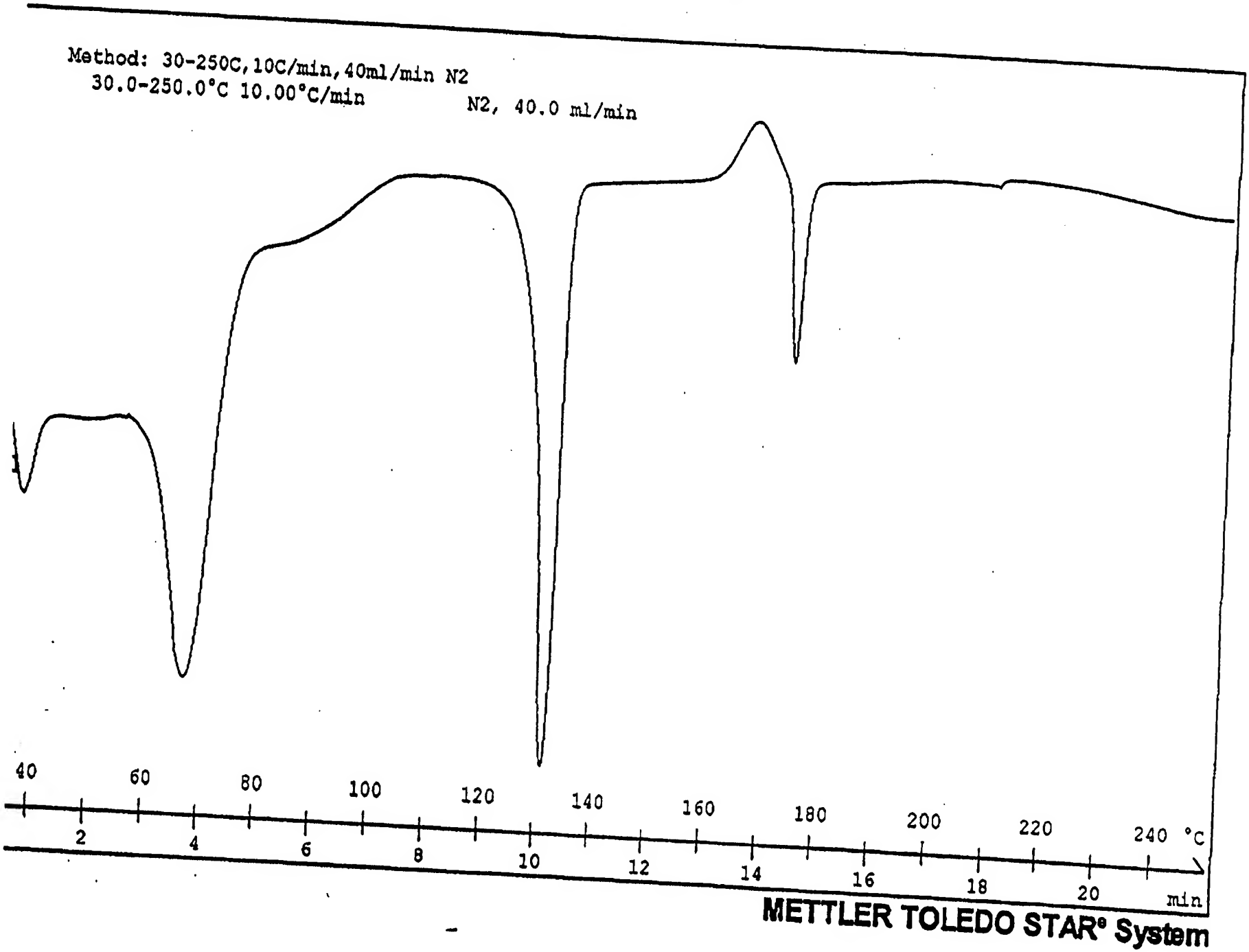
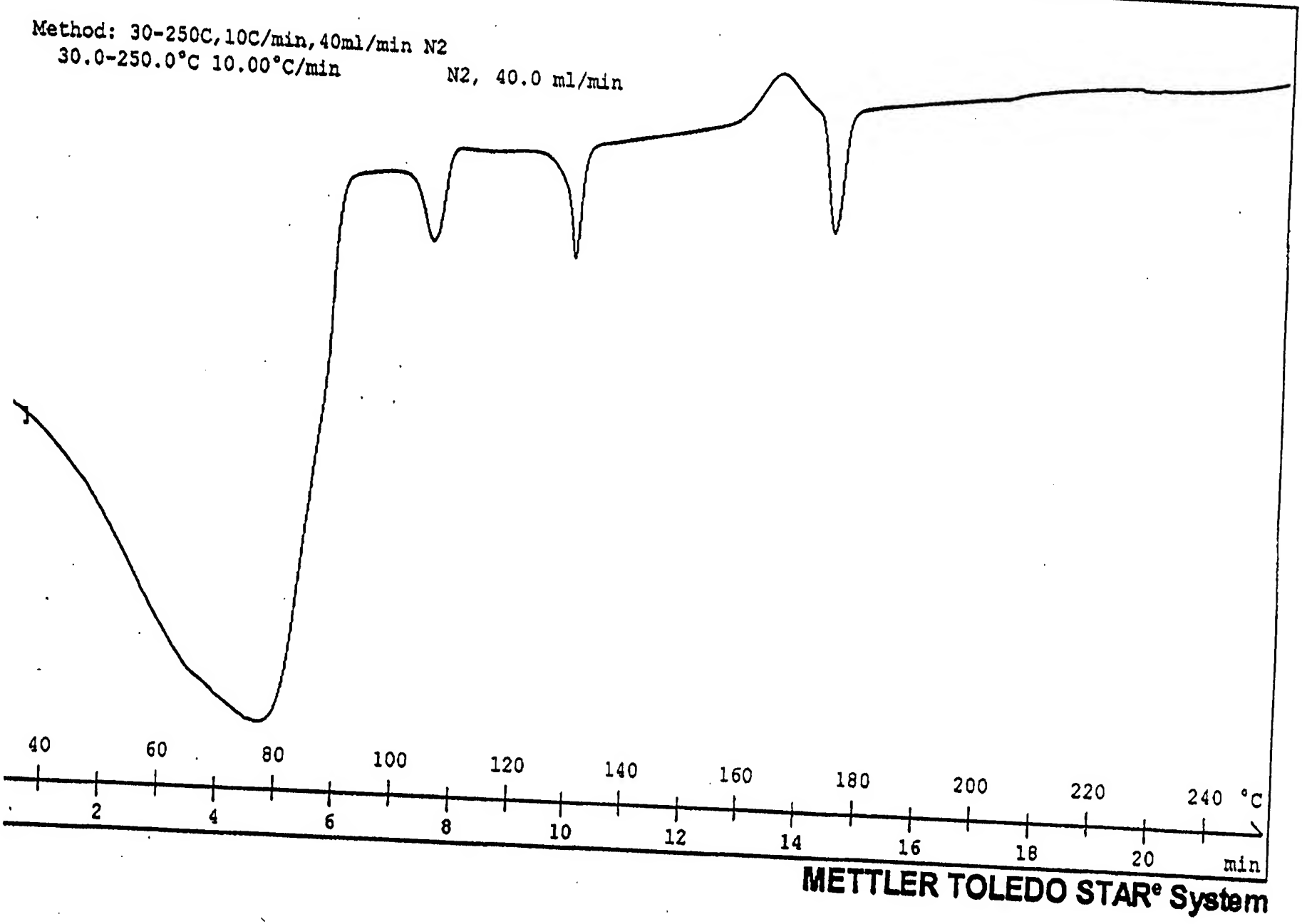


FIGURE 38

Form E



FIGURE

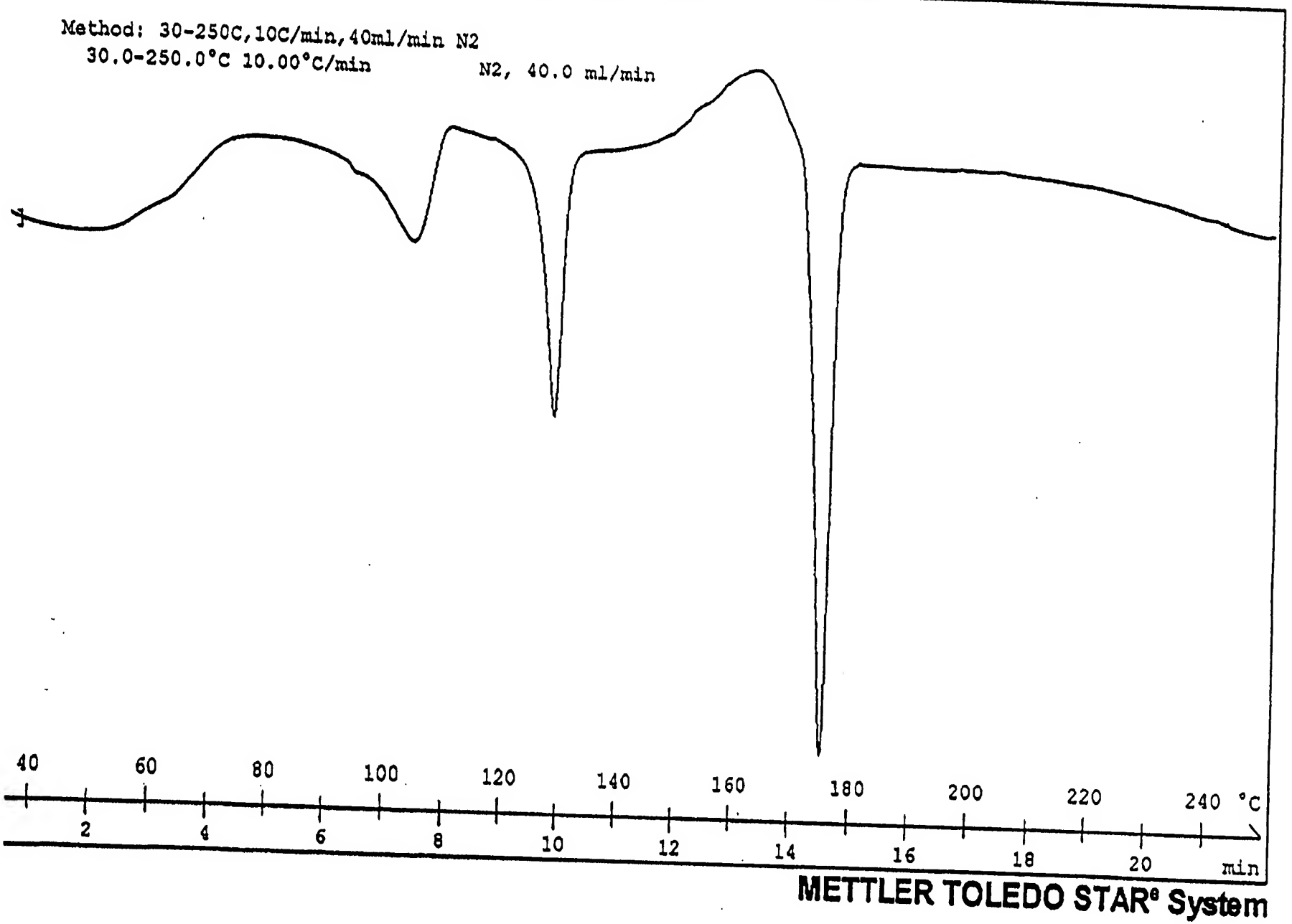
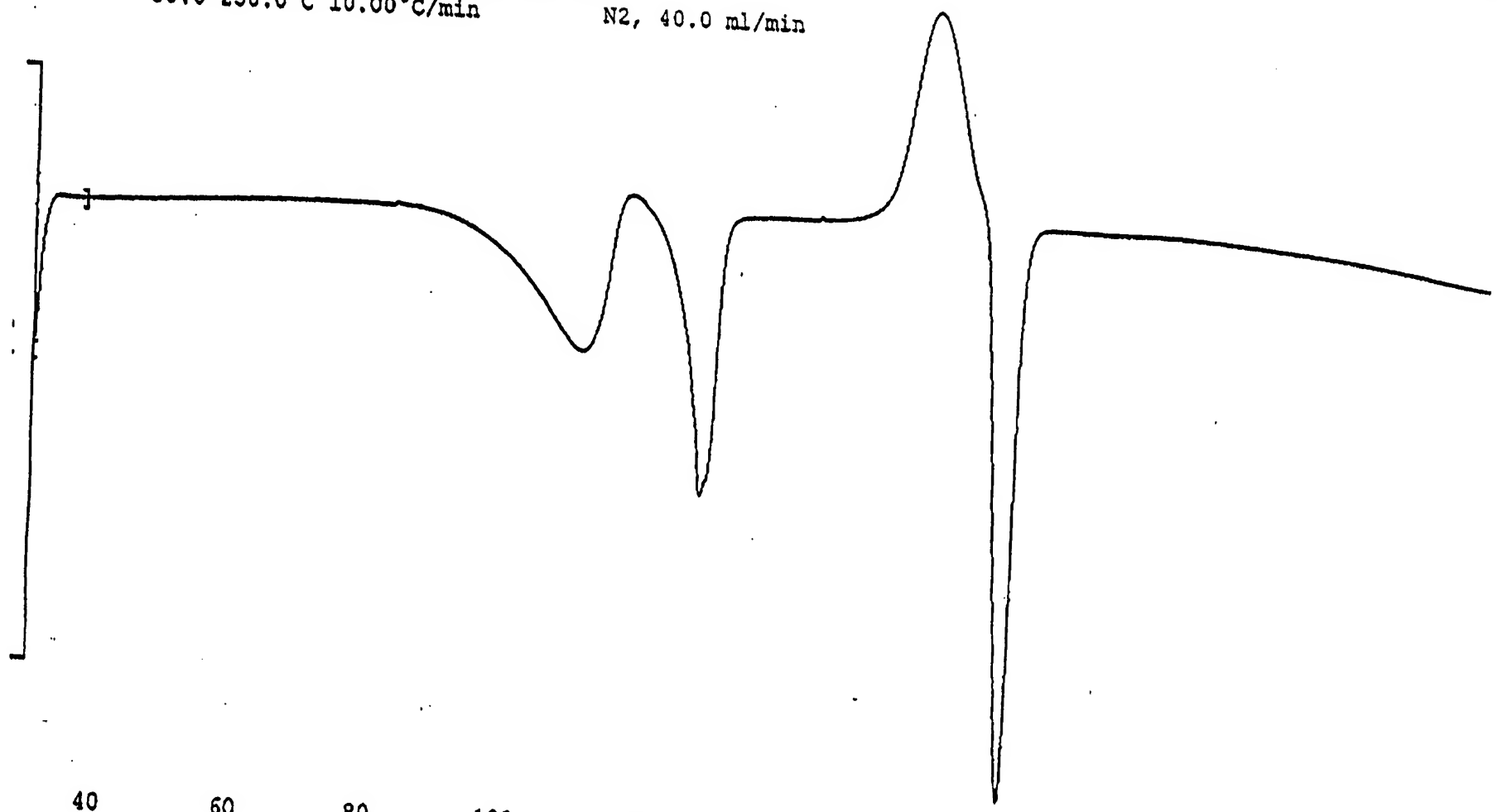

Method: 30-250C,10C/min,40ml/min N2
30.0-250.0°C 10.00°C/min
N2, 40.0 ml/min
40
60
80
100
120
140
160
180
200
220
240 °C
2
4
6
8
10
12
14
16
18
20
min
METTLER TOLEDO STAR° System

FIGURE 88

EXO

Method: 30-250C, 10C/min, 40ml/min N2
30.0-250.0°C 10.00°C/min N2, 40.0 ml/min



40 60 80 100 120 140 160 180 200 220 240
0 2 4 6 8 10 12 14 16 18 20 m

METTLER TOLEDO STAR° Syst

FIGURE 41

Form I

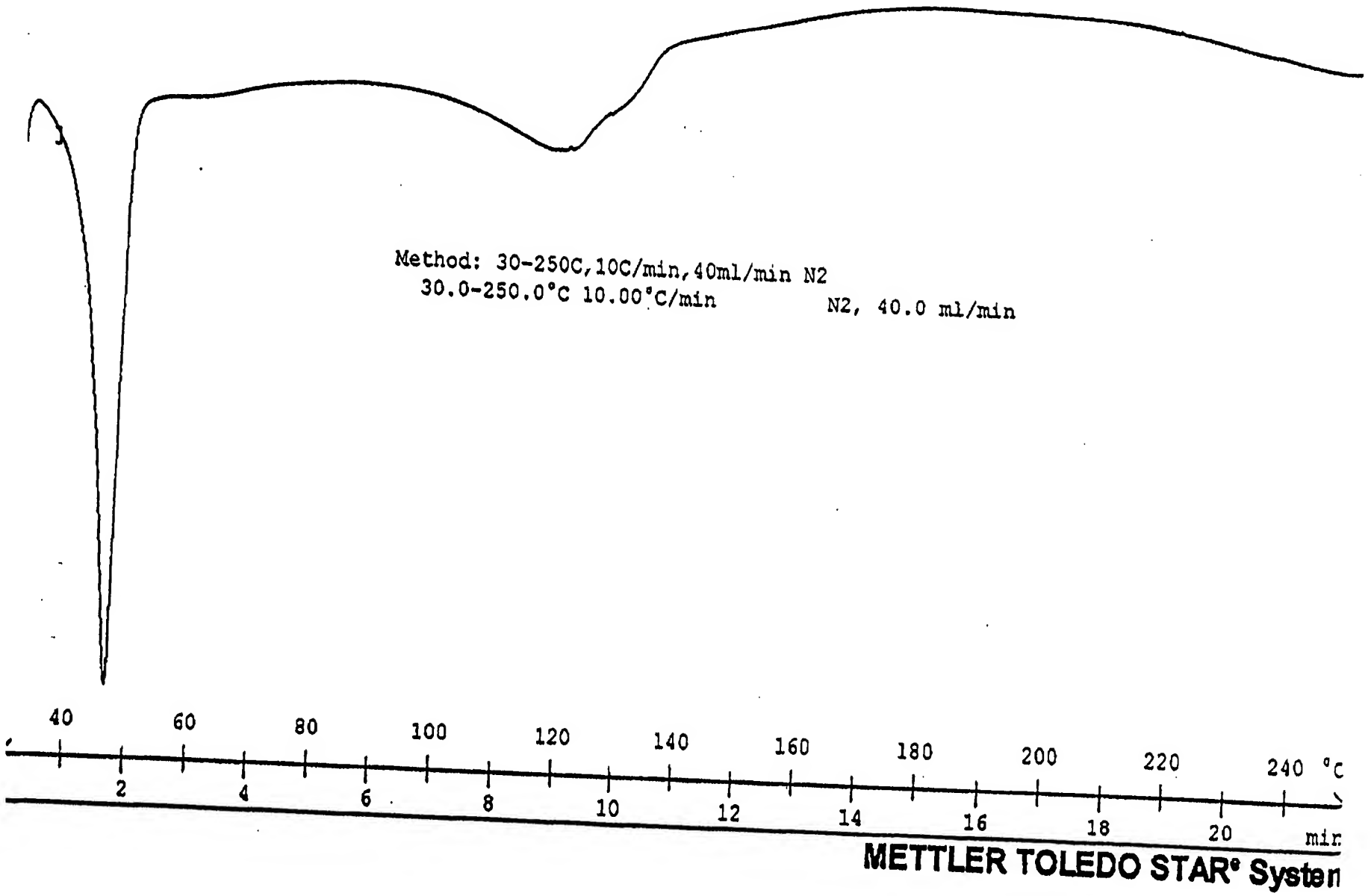


FIGURE 42

Form J

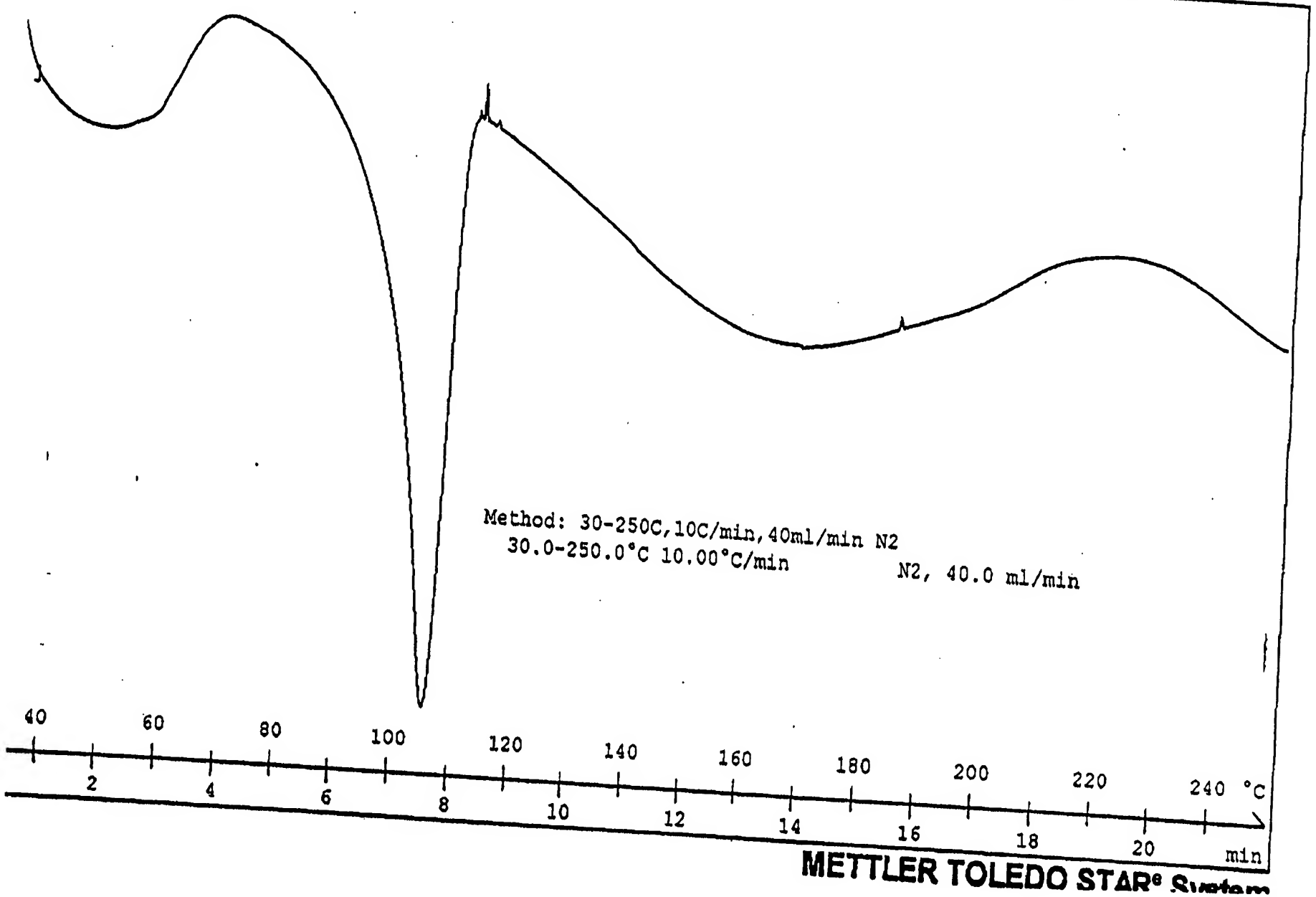


FIGURE 43

Form K

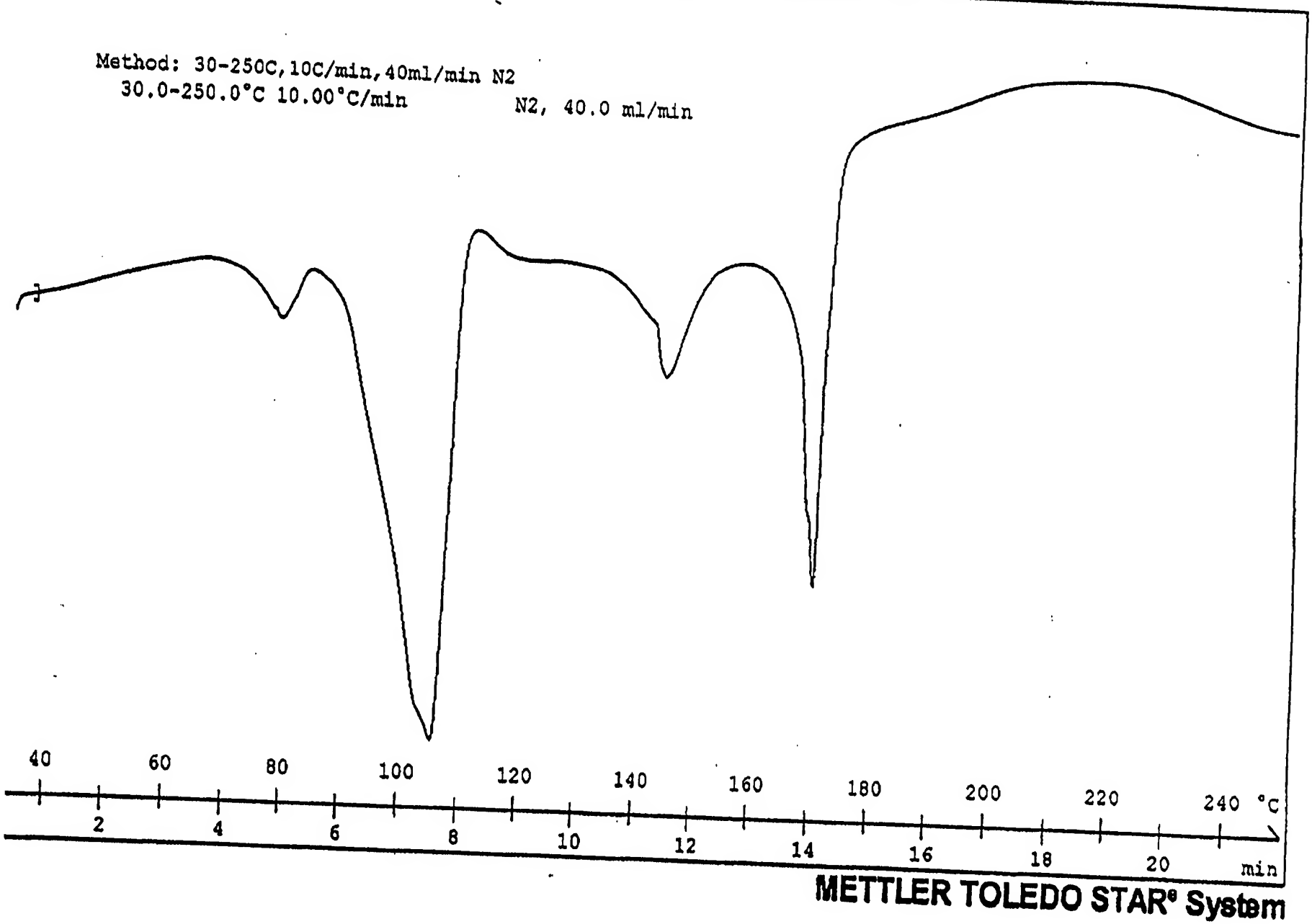


FIGURE ~~42~~ 4/4

Form L

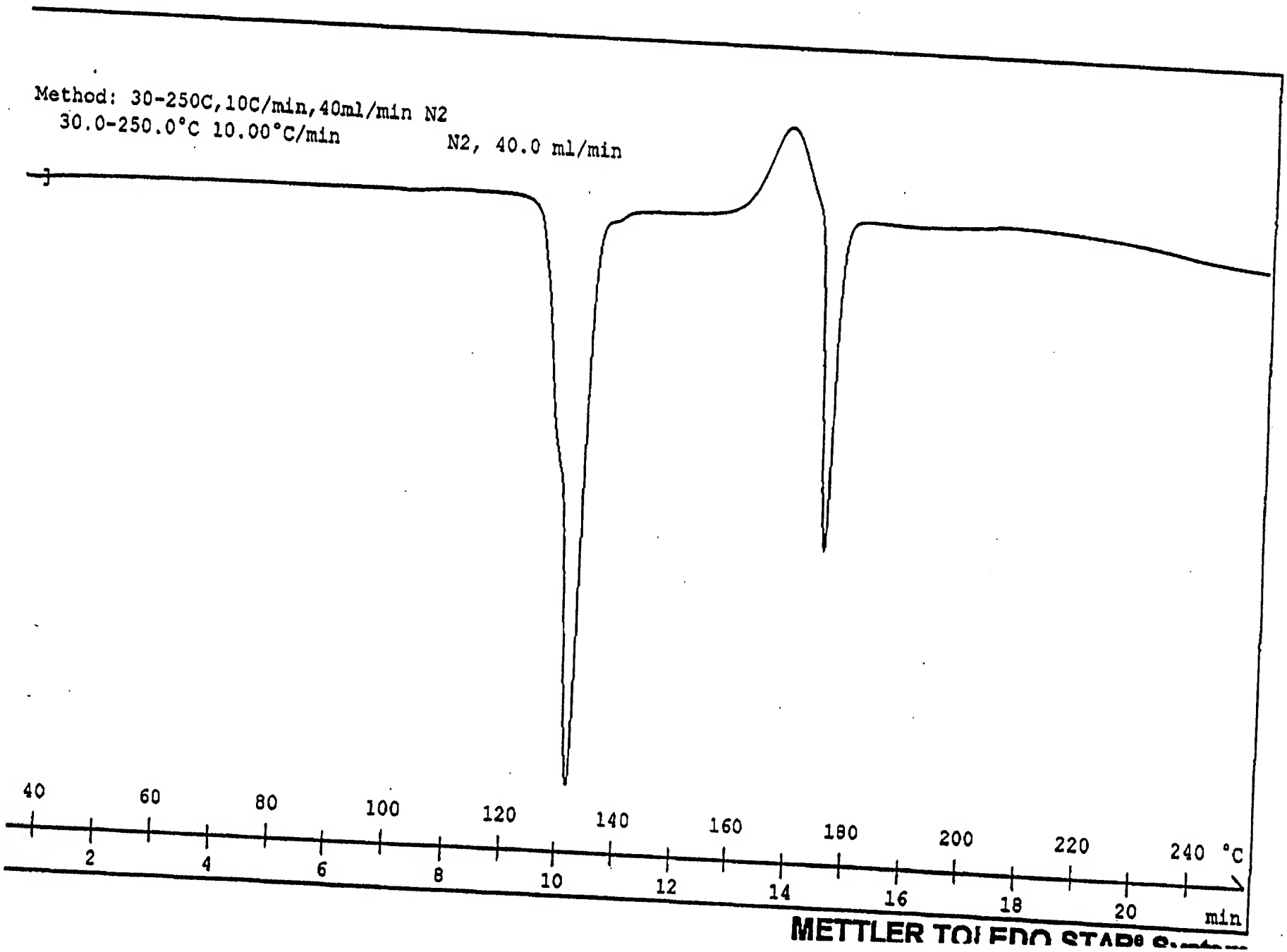


FIGURE 45
Form M

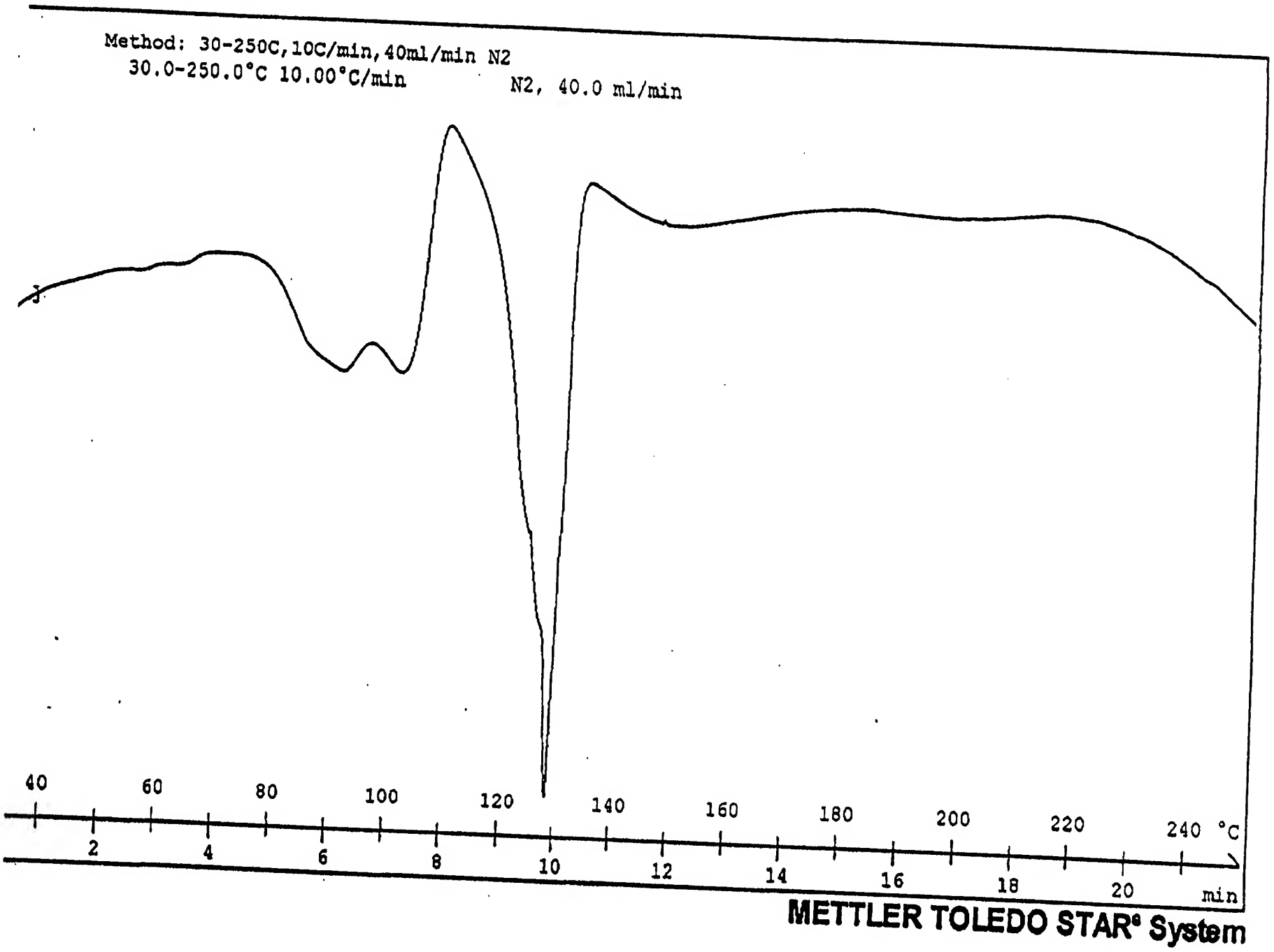


FIGURE ~~44~~ 46

Form N

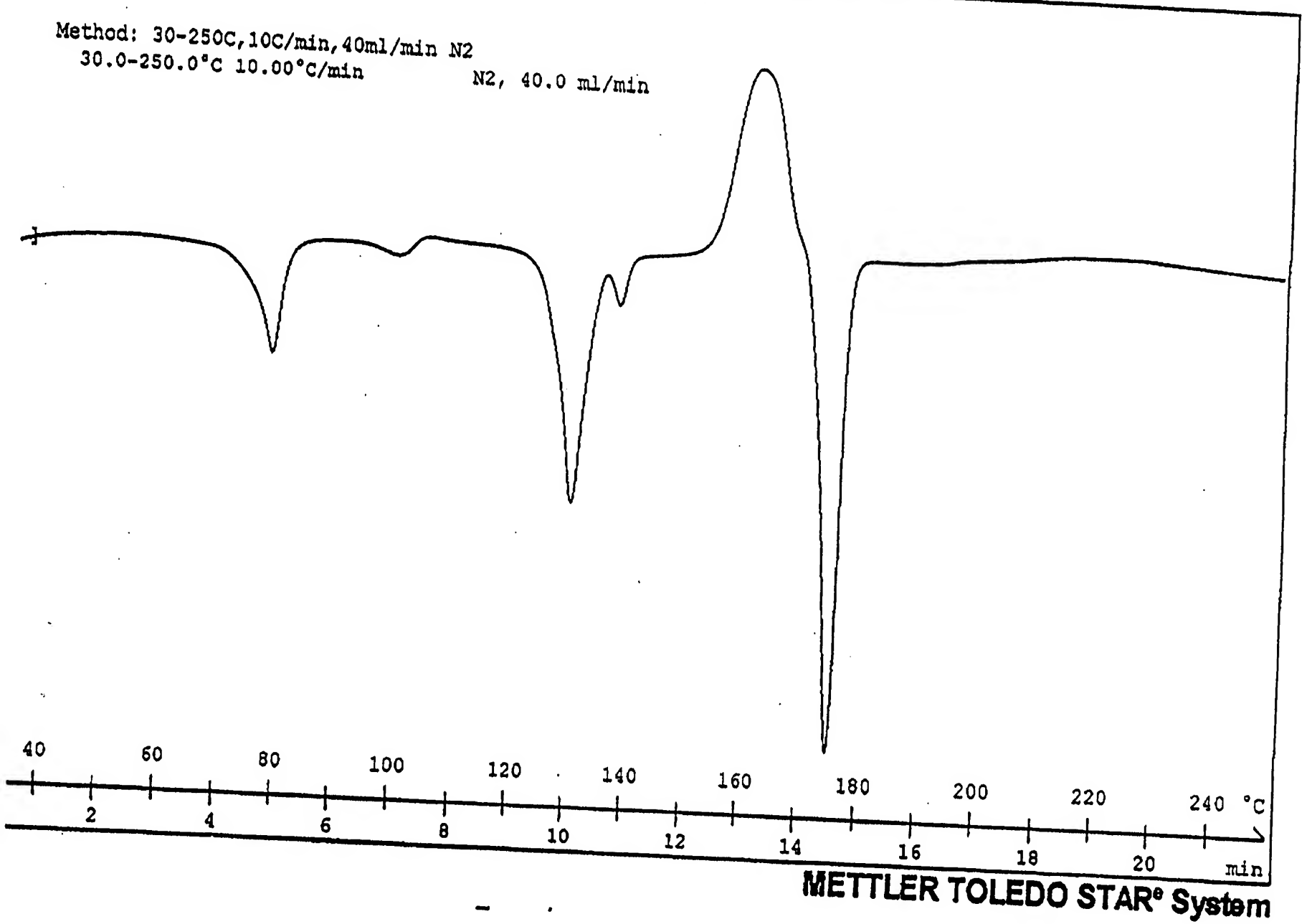


FIGURE ~~45~~ 47

Form G

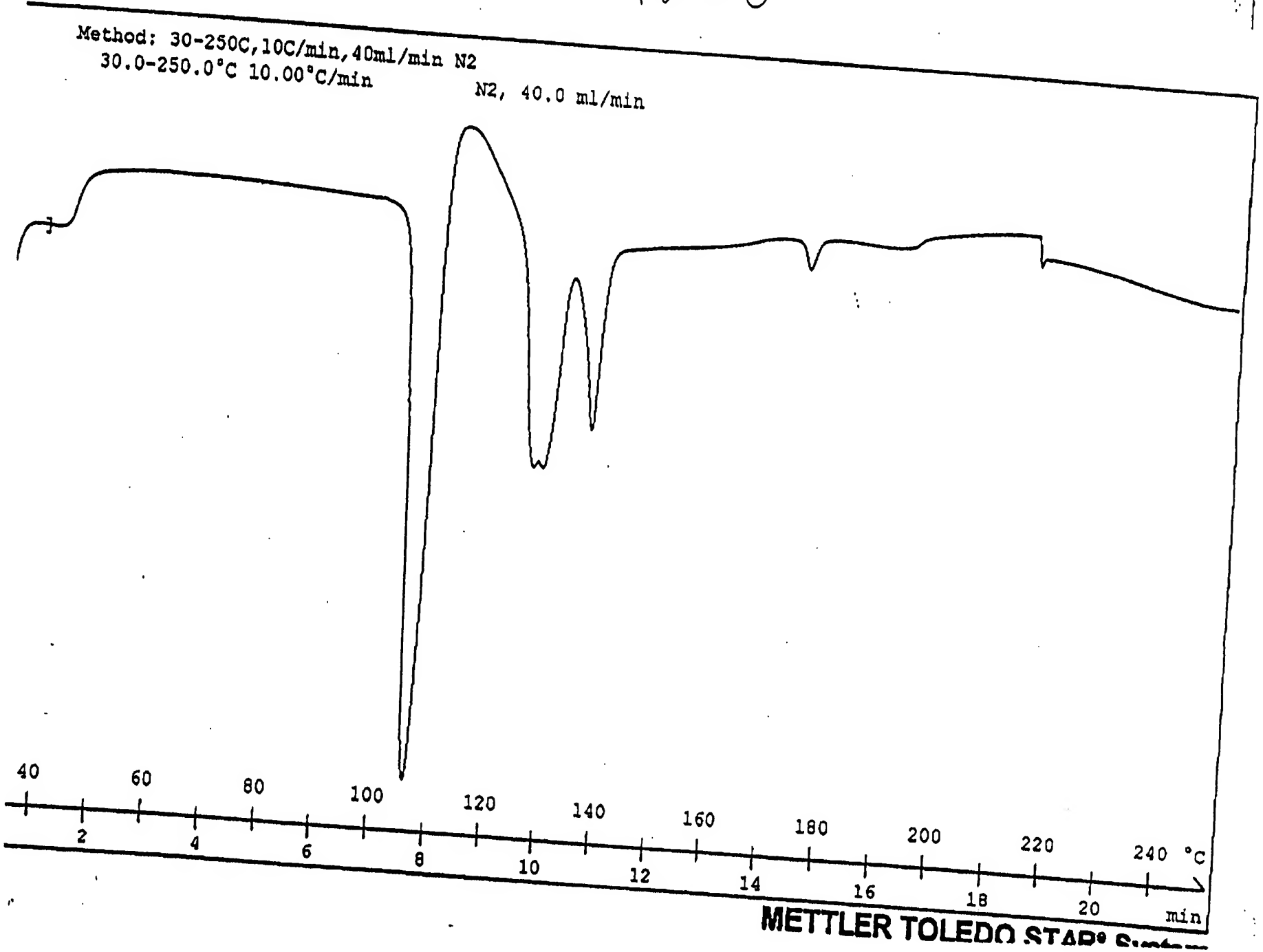


Figure 48
Form P

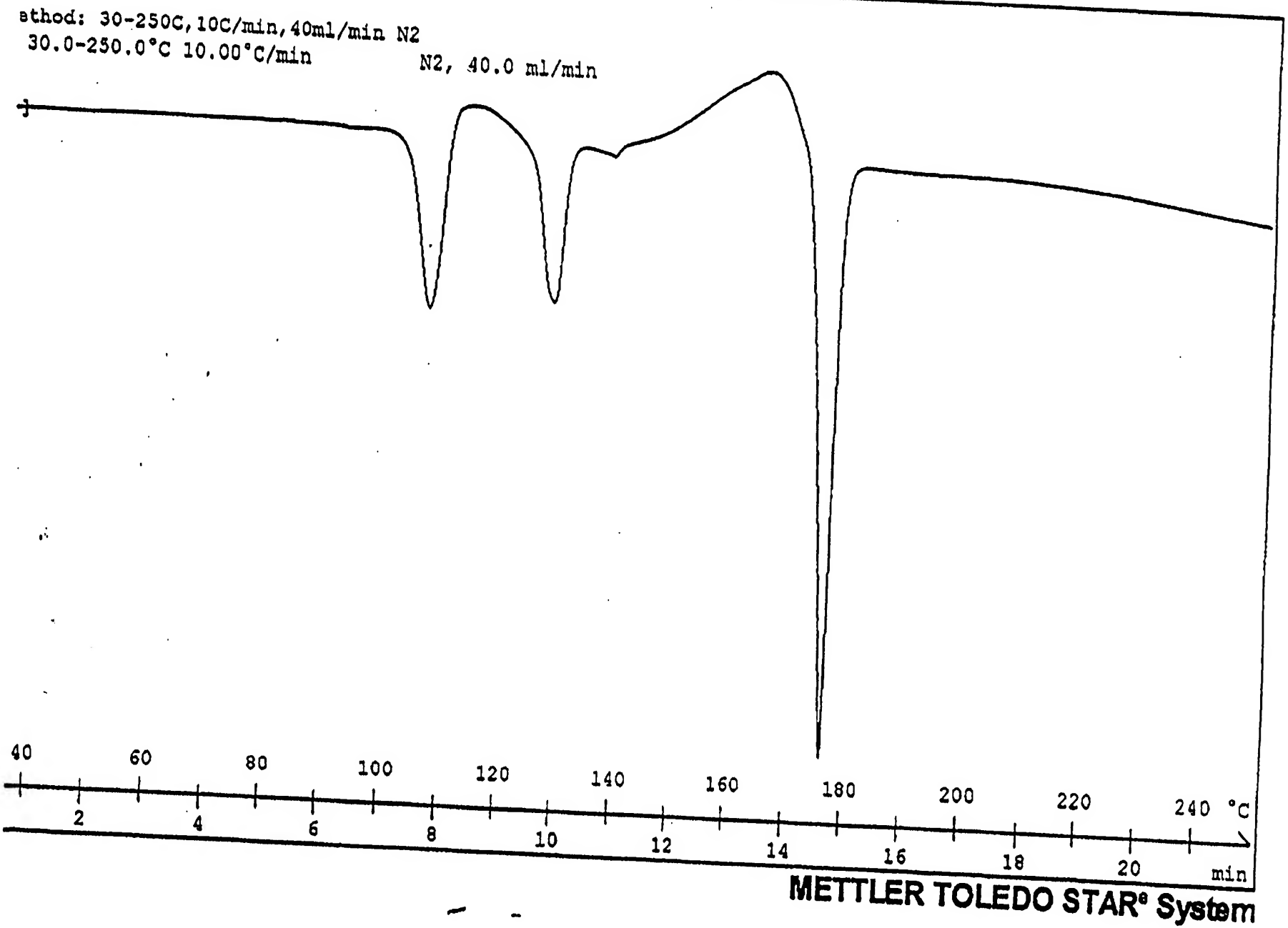


FIGURE ~~47~~ 49

Form Q

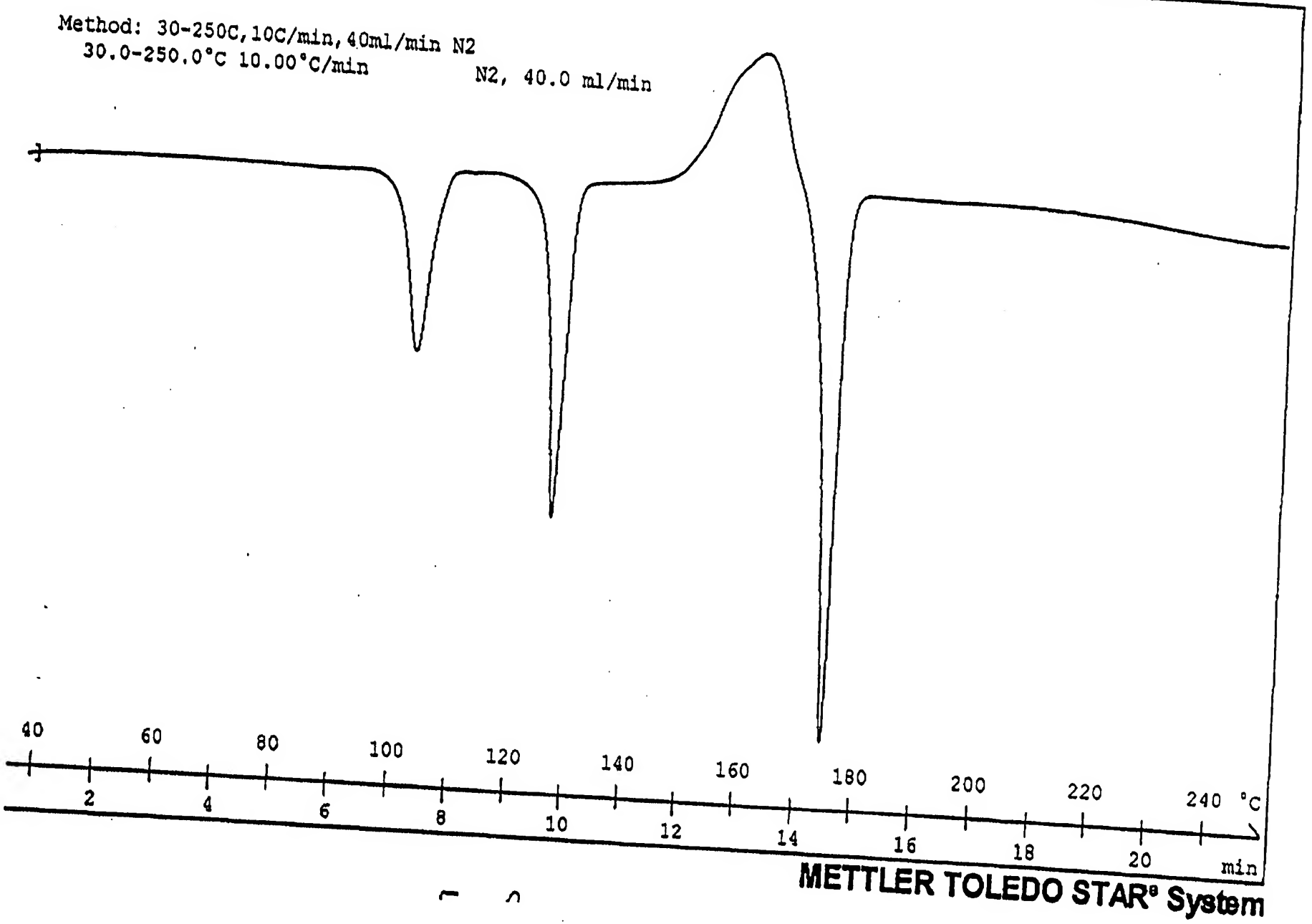


FIGURE ~~48~~ 50
Form T

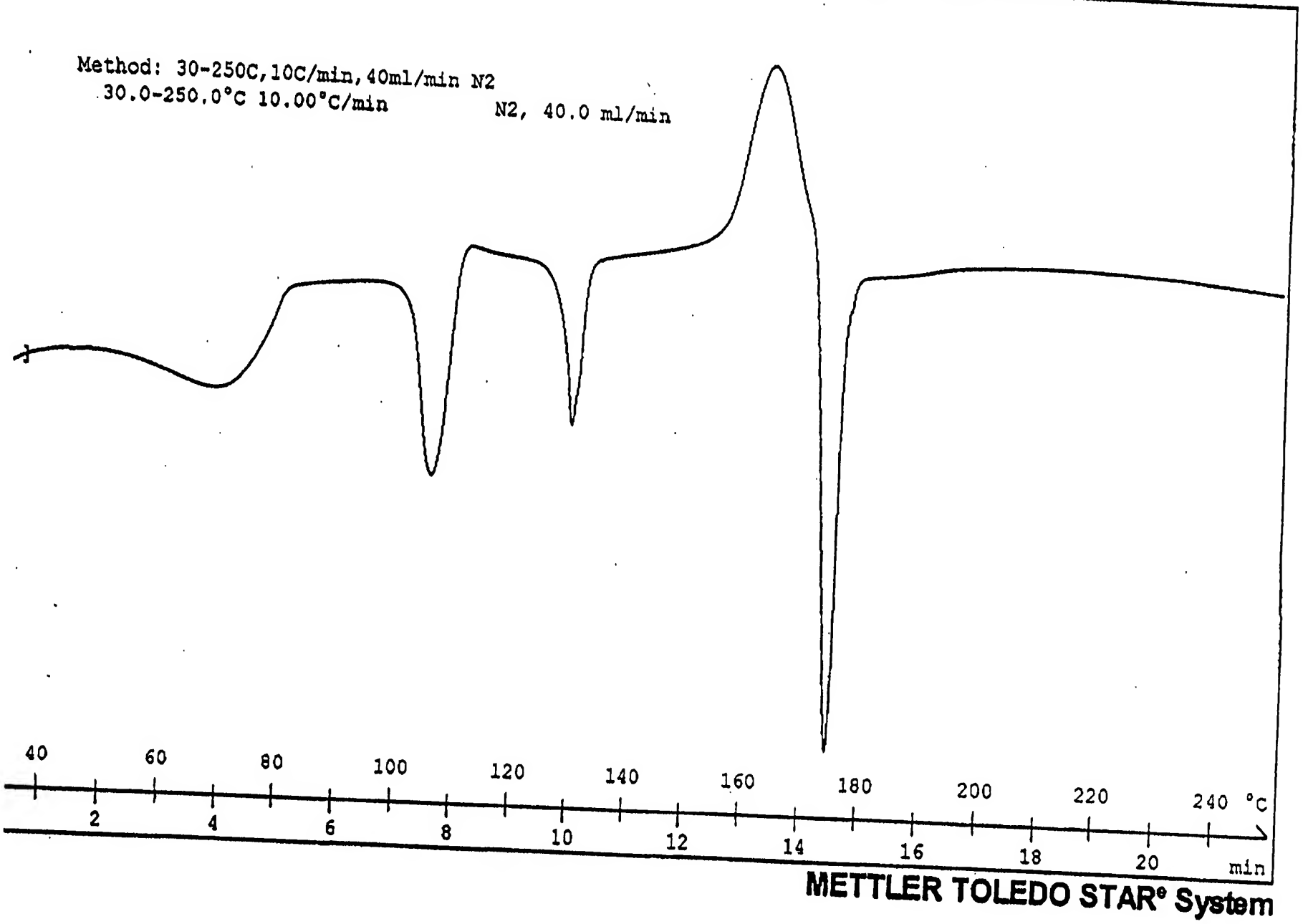


FIGURE ~~49~~ 51

Form 1

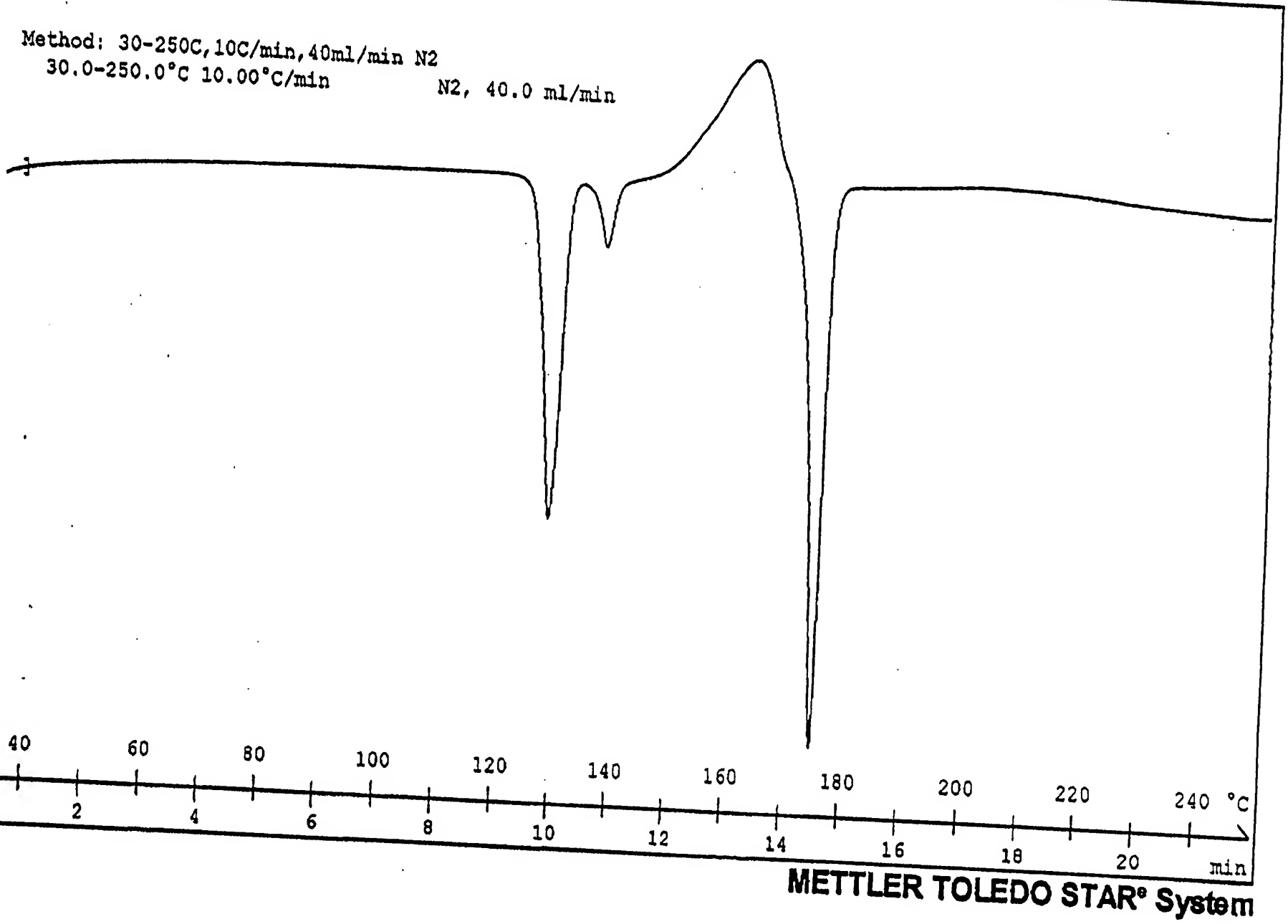


FIGURE ~~50~~ 52

Form V

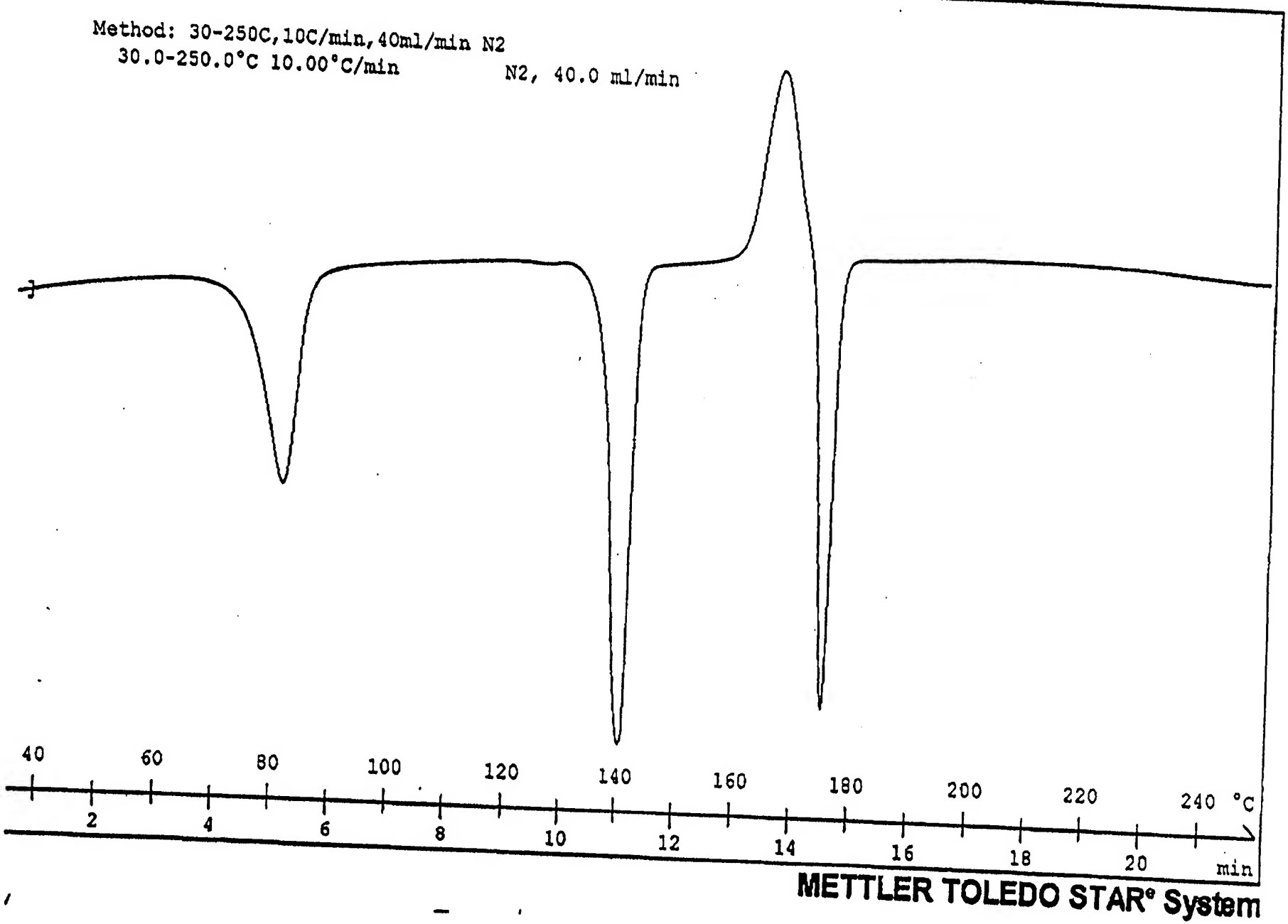


FIGURE ~~52~~ 53

Form Y (chloroform solvate)

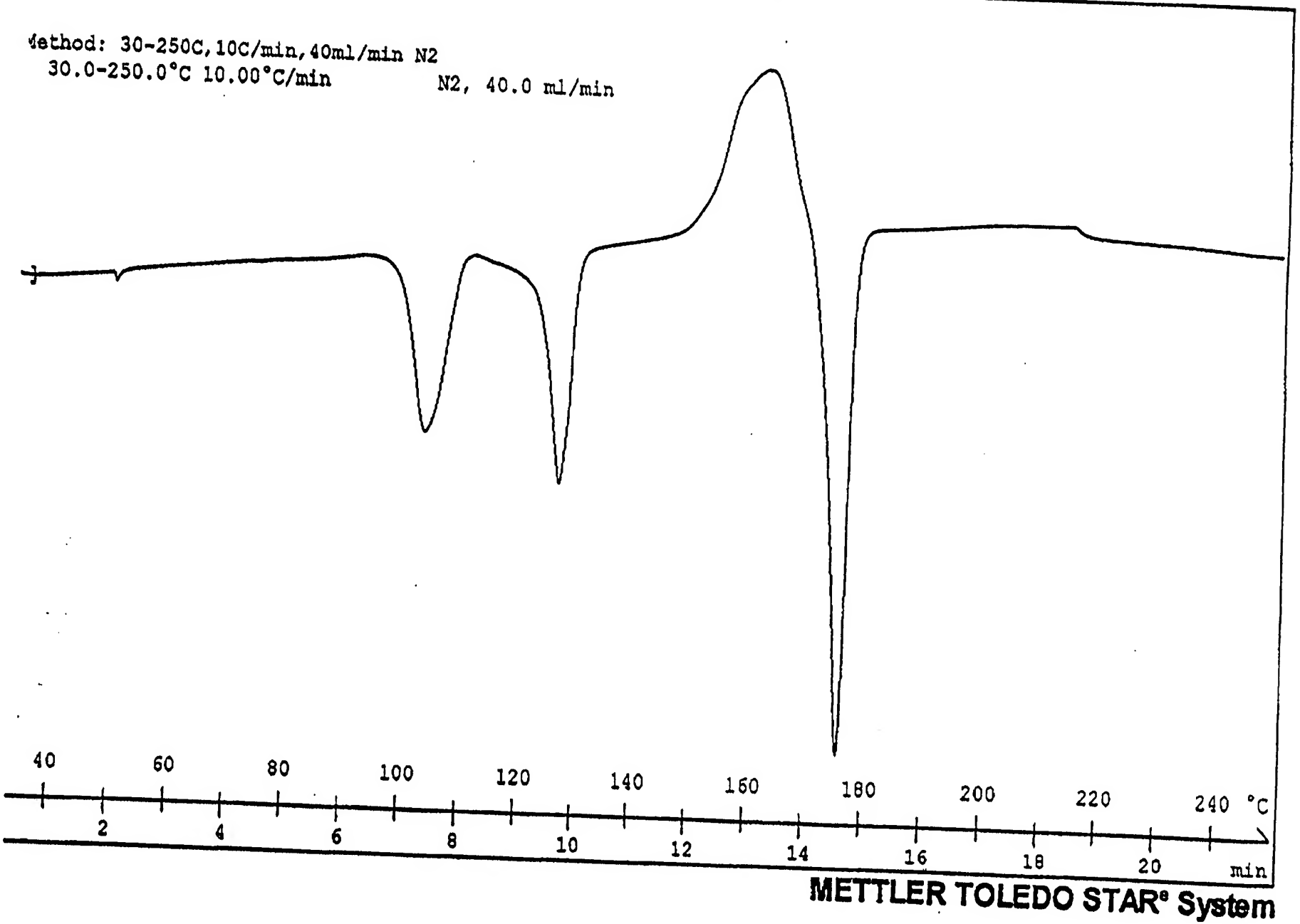


FIGURE 54
Y (dichloromethane solvate)

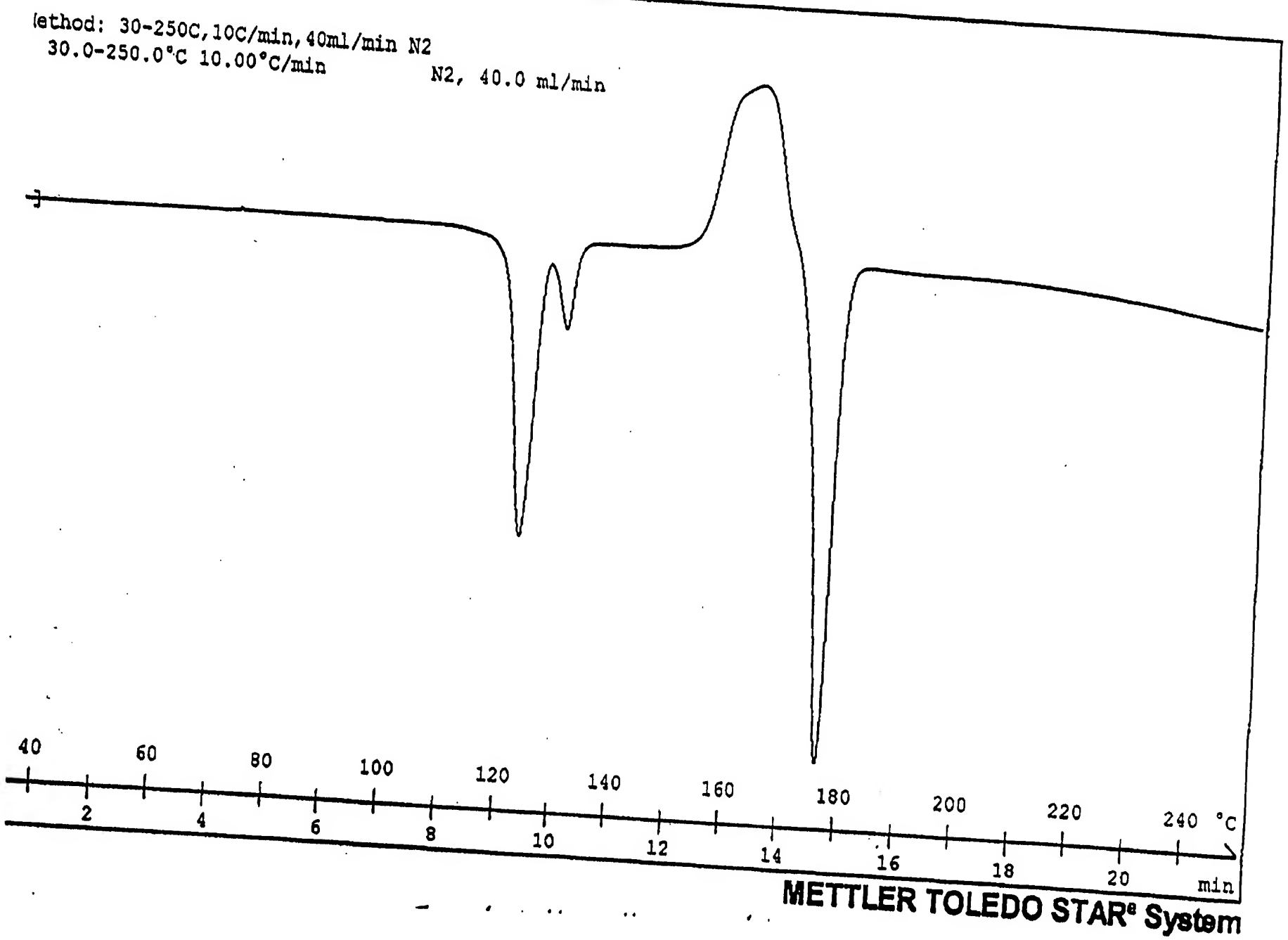


Figure ~~27~~ - Nateglinide Form Z

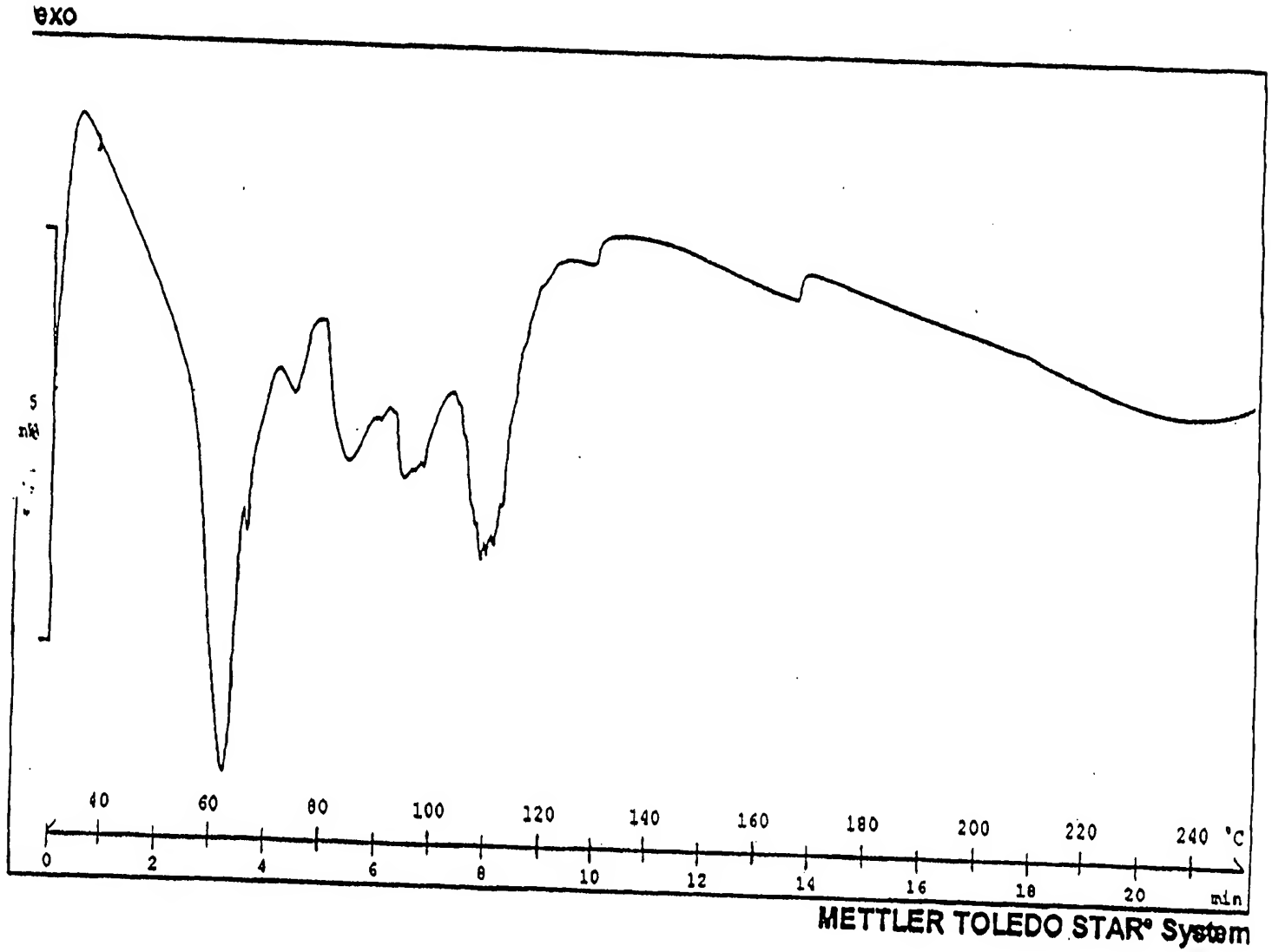


FIGURE ~~51~~ 56
Form α

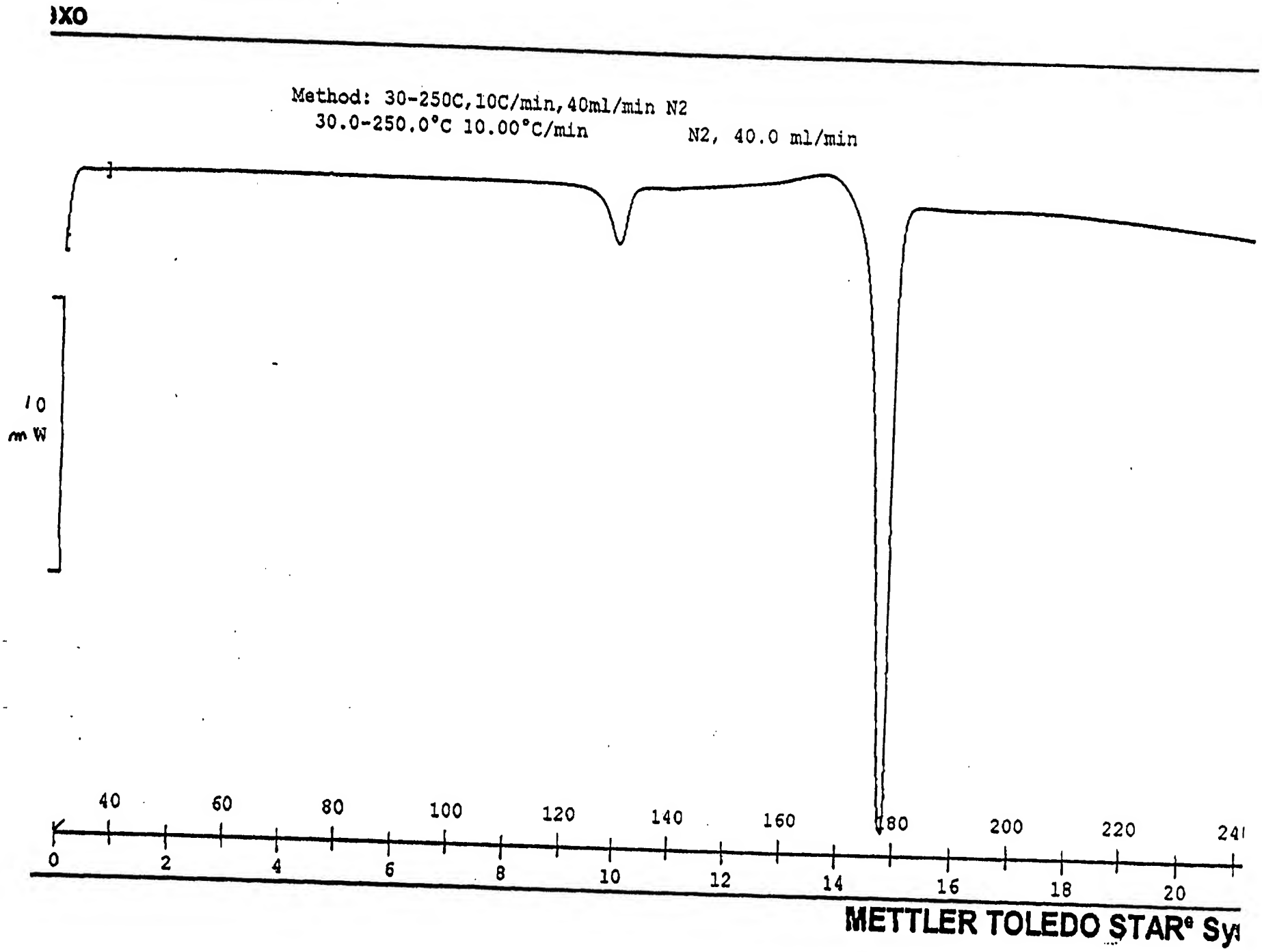


FIGURE ~~54~~ 57

Form Beta

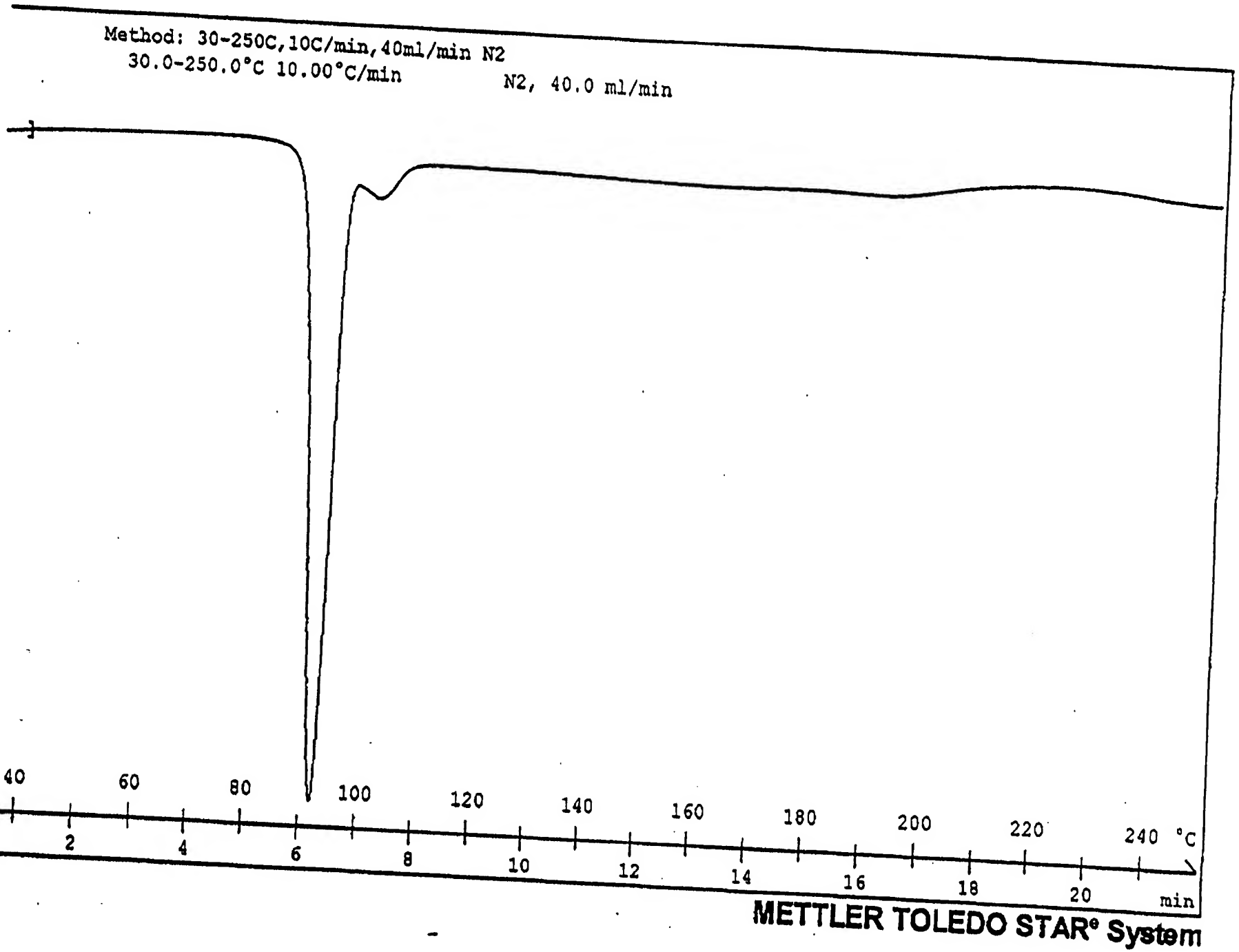
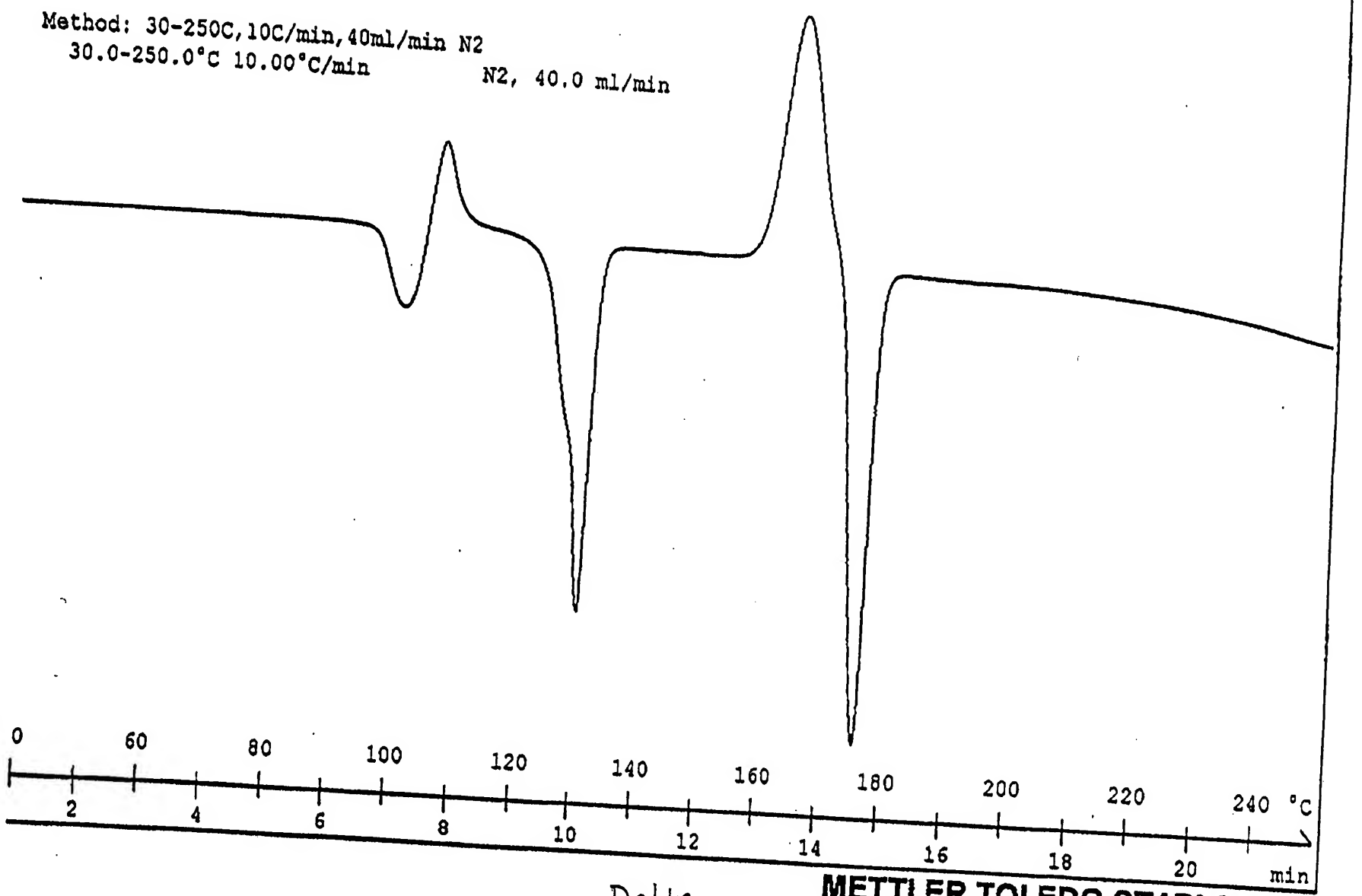


FIGURE ~~55~~ 58

Form Delta




- Delta

Form Epsilon FIGURE ~~56~~ 59

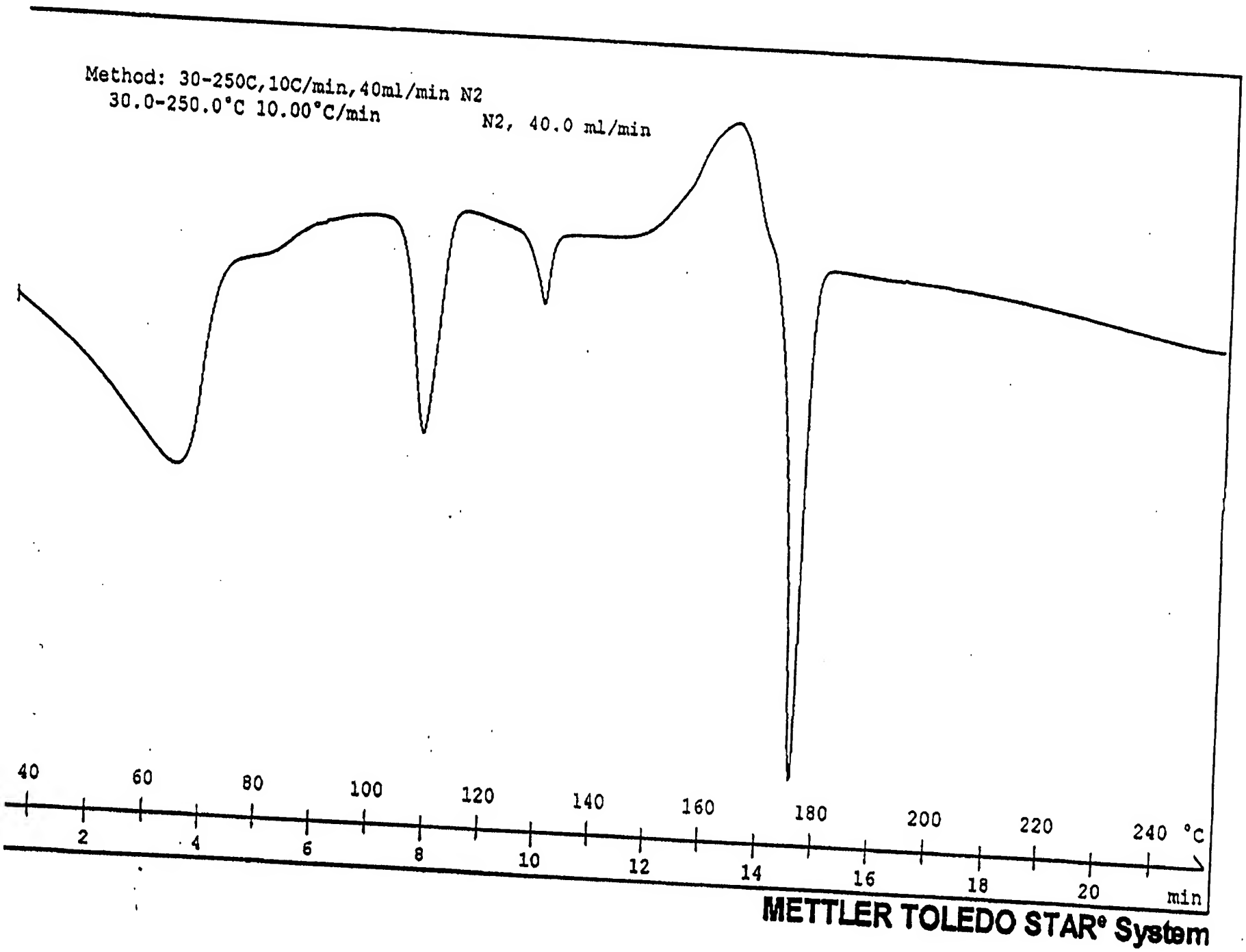
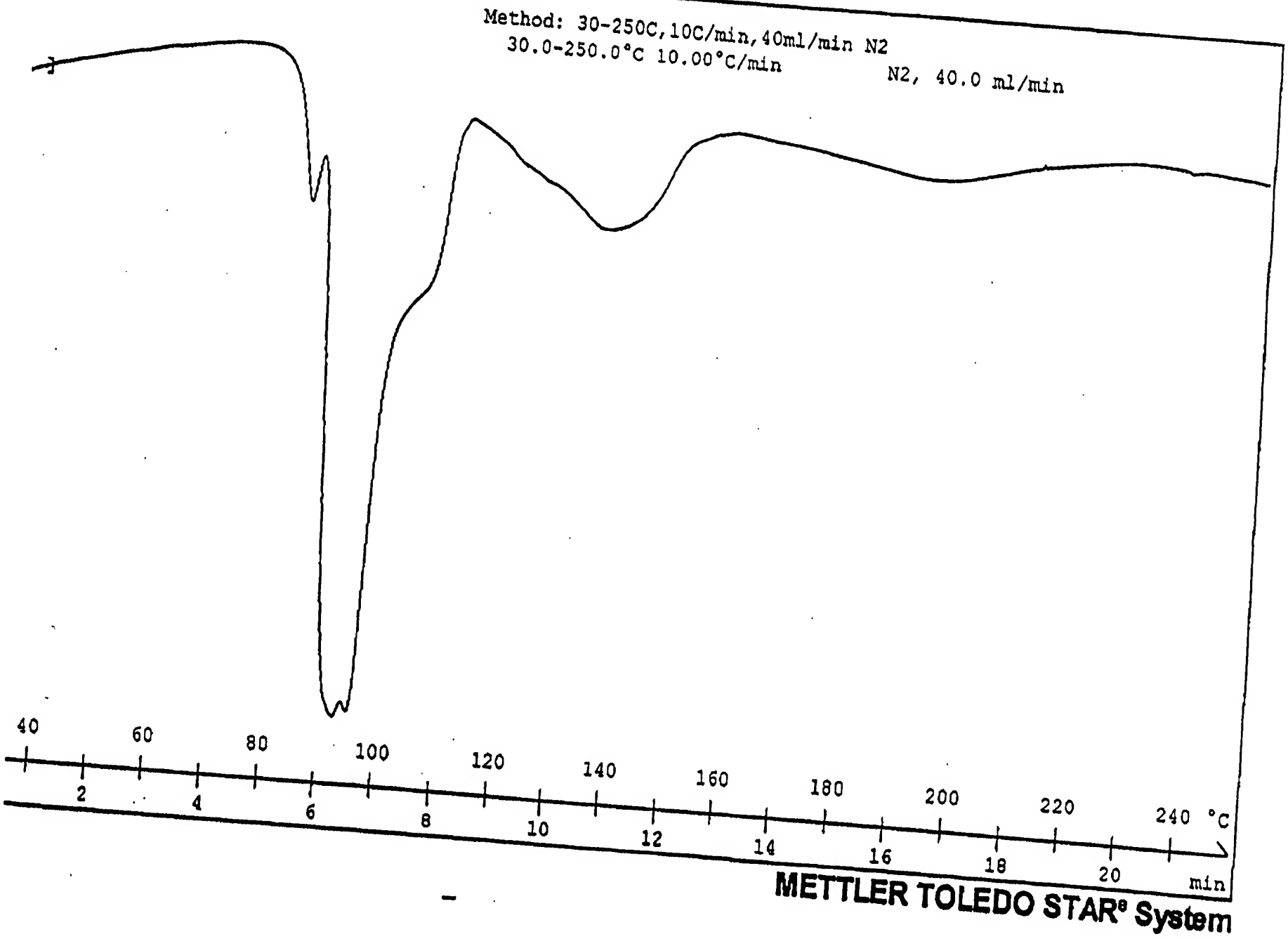
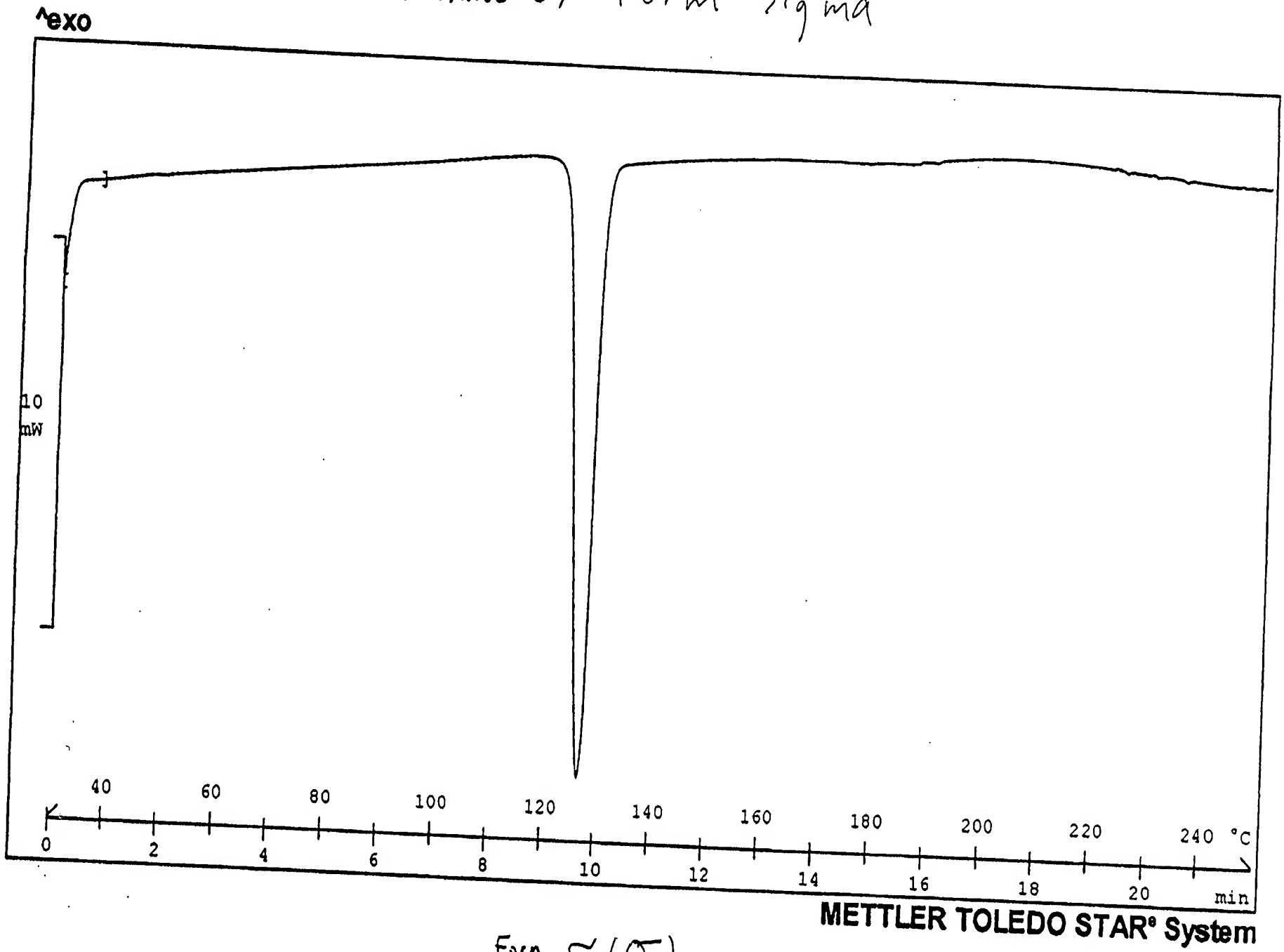


FIGURE ~~57~~ 60

Form Gamma

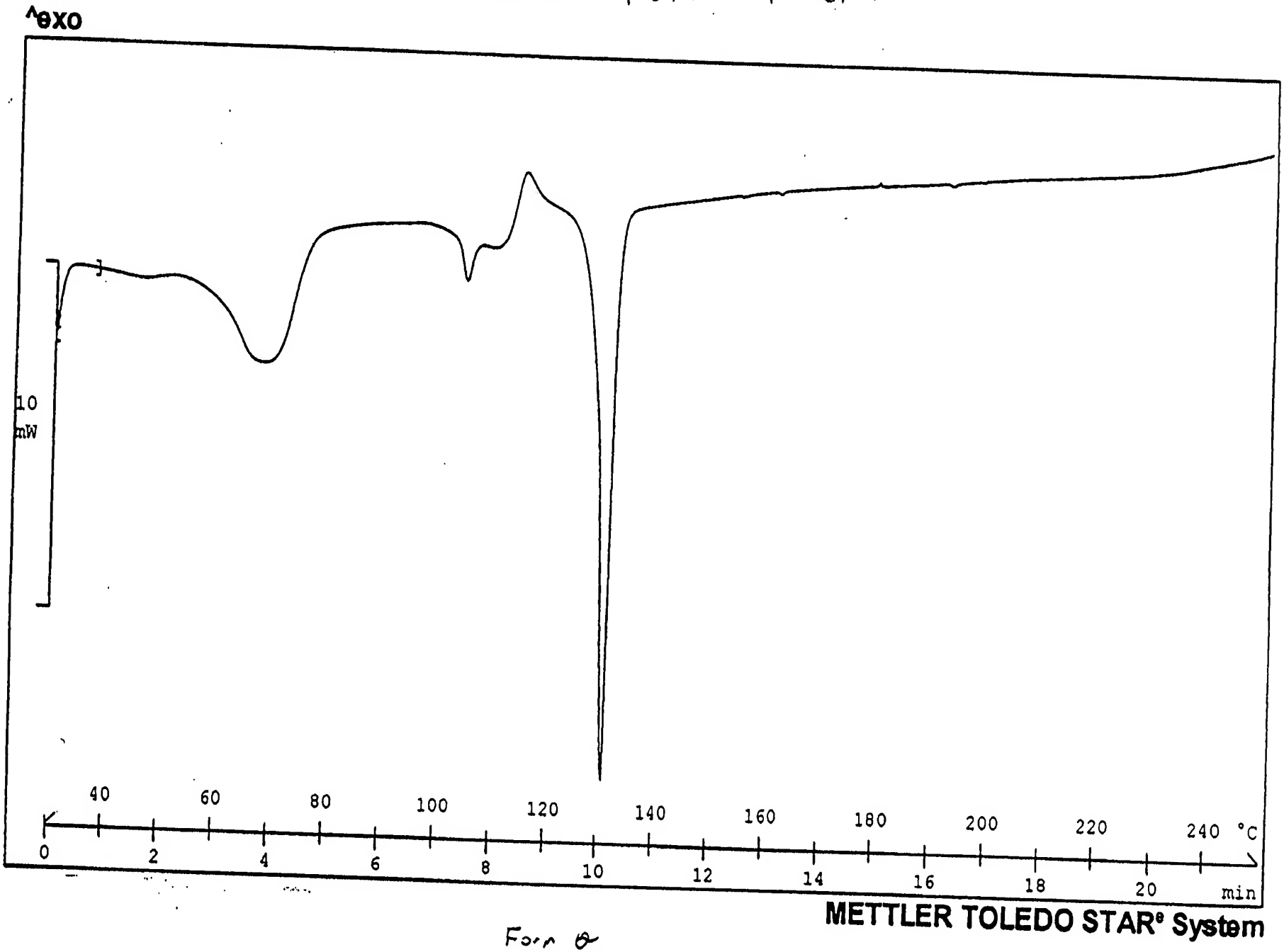


PIGURE 61 Form Sigma




Form ~ (σ)

FIGURE ~~59~~ 62 Form Theta




Form θ

Figure 63

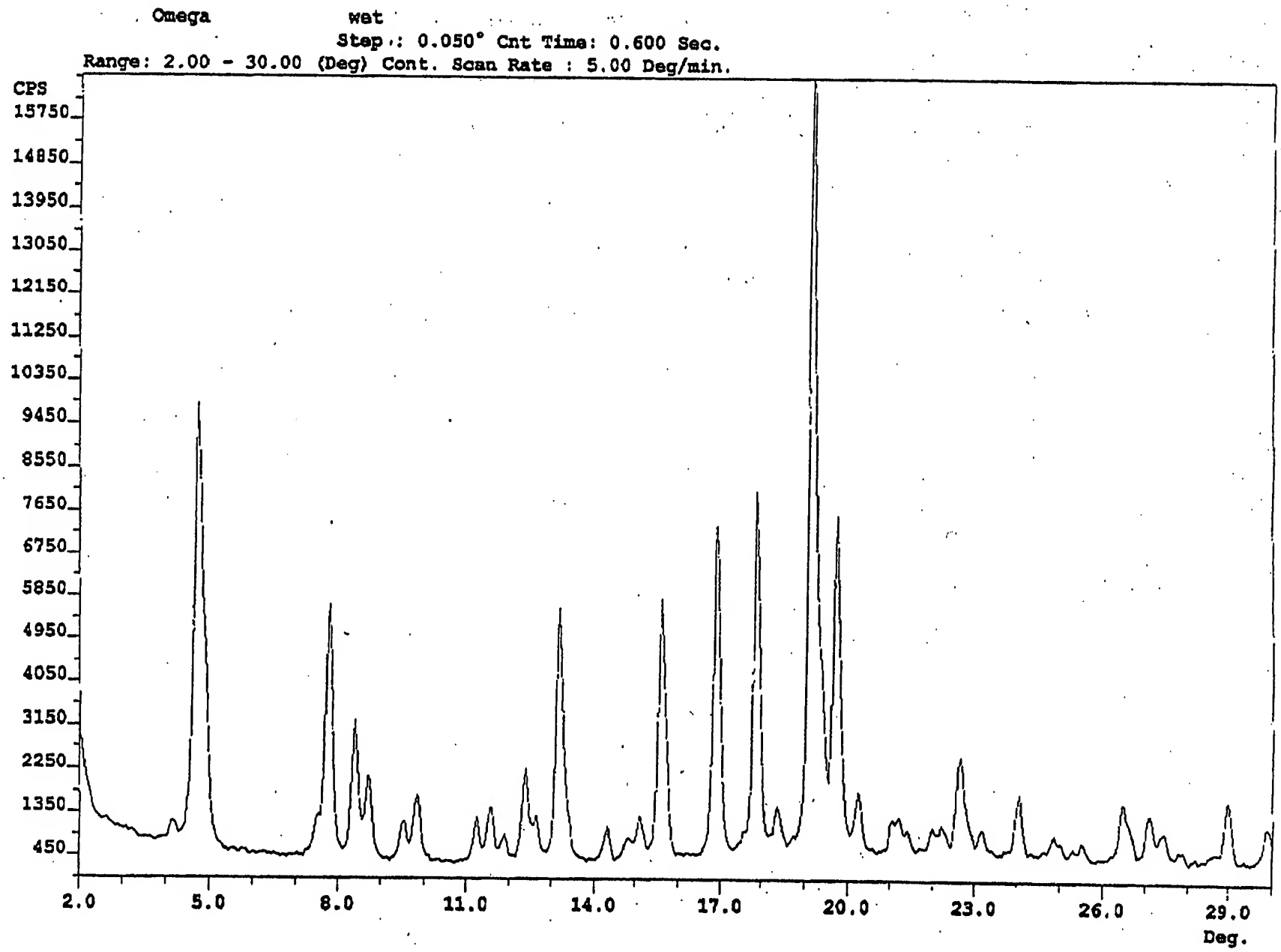

Omega
wet
Step : 0.050° Cnt Time: 0.600 Sec.
Range: 2.00 - 30.00 (Deg) Cont. Scan Rate : 5.00 Deg/min.
CPS
15750
14850
13950
13050
12150
11250
10350
9450
8550
7650
6750
5850
4950
4050
3150
2250
1350
450
2.0
5.0
8.0
11.0
14.0
17.0
20.0
23.0
26.0
29.0
Deg.

**Figure 64**

**Comparison between the impurity profile of Nateglinide crystallized in IPA-$H_2O$ and Nateglinide crystallized in Methanol-$H_2O$**

| Sample No | Solvent | Impurity prfile by RRT [% w/w] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | D-PA (0.23) | (0.25) | (0.46) | (0.80) | Ipcha (0.89) | Dimer (1.38) | Methyl Ester (1.51) | (1.76) | Isopropyl Ester (2.3) |
| RL-2155/1 | Methanol-$H_2O$ | <0.01 | | 0.02 | <0.01 | 0.03 | 0.02 | 2.91 | 0.04 | |
| RL-2163/4 | IPA-$H_2O$ | <0.01 | 0.04 | | 0.02 | 0.02 | 0.01 | | 0.03 | 0.02 |

Note: D-PA means D-Phenyl Alanine
Ipcha means Iso propyl cyclohexyl carboxylic acid

Both are the starting materials of the product

(-)-N-[(trans-4-isopropyl cyclohexane)carbonyl]-D-phenylalanine